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(54) AMIDES OF HYALURONIC ACID AND THE DERIVATIVES THEREOF AND A PROCESS FOR THEIR PREPARATION

HYALURONSÄUREAMIDE UND IHRE DERIVATE UND EIN VERFAHREN ZU DEREN HERSTELLUNG

AMIDES D'ACIDE HYALURONIQUE, DERIVES DE CE DERNIER ET LEURS PROCEDE DE PREPARATION

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(56) References cited:
EP-A- 0 506 976
WO-A-89/02445
WO-A-92/20349

- **DANISHEFSKY ET AL: 'CONVERSION OF CARBOXYL GROUPS OF MUCOPOLYSACCHARIDES INTO AMIDES OF AMINO ACID ESTERS' CARBOHYDRATES RESEARCH vol. 16, 1971, pages 199 - 205**

EP 1 095 064 B1

Description

SUBJECT OF THE INVENTION

[0001] The present invention is directed to amides of hyaluronic acid and derivatives thereof for the preparation of pharmaceutical formulations, of biomaterials and for the coating of biomedical objects and the process for their preparation.

FIELD OF THE INVENTION

[0002] Hyaluronic acid is a heteropolysaccharide composed of alternate residues of D-glucuronic acid and N-acetyl-D-glycosamine. It is a straight-chained polymer the molecular weight of which varies between 50,000 and 13,000,000 Da depending on the source from which it was obtained and the methods used to obtain it. It is present in nature in pericellular gels, in the fundamental substance of the connective tissue of vertebrate organisms of which it represents one of the main components, in the synovial fluid of the joints, in the vitreous humor, in the human umbilical cord tissues and in rooster combs.

[0003] In recent years, numerous types of hyaluronic acid derivatives have been synthesised to obtain compounds with pharmacological properties, or compounds that can be processed in various forms of biodegradable and biocompatible biomaterials for use in various fields of medicine, surgery and tissue engineering.

[0004] Among the amide derivatives reported in the state of the art are known water-insoluble compositions constituted by mixtures deriving from the reaction between the carboxyl of hyaluronic acid, a nucleophil, such as an aminic compound, and an activating agent (US 5,760,200; US 4,937,270). Such mixtures are mainly used in the prevention of post-surgical adhesions.

[0005] U.S. patent No. 5,733,891 describes pharmaceutical compositions containing amide derivatives of hyaluronic acid obtained by reaction of its carboxyls with basic anti-tumour agents. The purpose of these compounds is to focus the action of the active principle on the diseased tissues and to limit any harmful effects on the healthy tissues.

[0006] Moreover, there are known amides of glycosaminoglycans, such as hyaluronic acid, with photosensitive compounds bound by polyfunctional compounds that act as bridges in the formation of amide bonds (US 5,462,976).

[0007] Lastly, there is a known process for the preparation of insoluble amides by the reaction of active esters of hyaluronic acid with amines. (WO 95/24429).

[0008] The aim of the present invention is to provide isolated and characterised amides of hyaluronic acid or derivatives thereof, obtained by reacting the carboxy groups or amino groups originating from deacetylation reactions, with amines and acids of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series respectively, and without the use of spacer chains.

[0009] Said compounds can be either water soluble or insoluble, according to the acid, the amine, the percentage of amide bond or the derivative of hyaluronic acid used to prepare the amide.

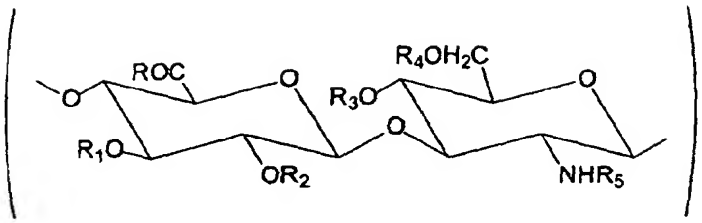
[0010] Therefore, the products according to the present invention are suitable for a large number of applications according to their solubility in water, their viscosity and the stability of the amide bond.

[0011] Indeed, said compounds can be used to prepare both pharmaceutical compositions and biomaterials. Moreover, they have the advantage of being able to be formed by reaction, not only with amines, but also with pharmacologically active acids.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention is directed to amidic, water-soluble compounds of hyaluronic acid and derivatives thereof for the preparation of pharmaceutical formulations, biomaterials and for the coating of biomedical objects and the process for their preparation.

[0013] The amidic, water-soluble compounds according to the present invention can be represented by the following general formula that represents the repetitive unit of the polymer:



wherein:

R = NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;

R_1, R_2, R_3, R_4= H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;

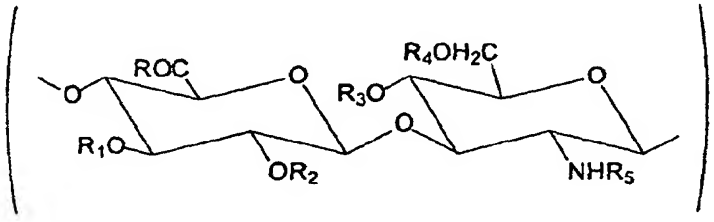
R_5 = -CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;

R_6 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

R_7 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group,
with the provisos that when R_6 is H, R_7 is not -$CH_2CO_2CH_3$, and that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

[0014] In another aspect, the invention concerns pharmaceutical compositions containing amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R= NR_6R_7, or alcoholic group of the aliphatic,
aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;

R_1, R_2, R_3, R_4= H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;

R_5 = -CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;

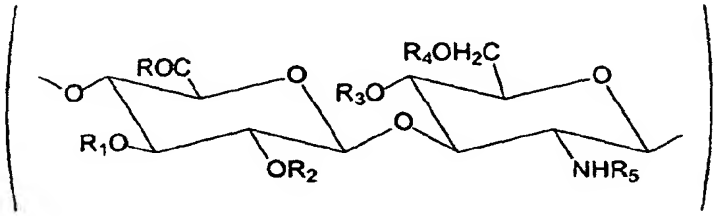
R_6 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

R_7 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group,
alone or in association with one another or with other pharmacologically active substances and in association with a

pharmaceutically acceptable carrier, with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

[0015] In a further aspect, the invention concerns biomaterials constituted by amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:

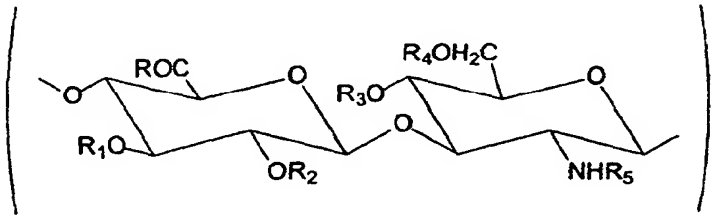


wherein:

R =	NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;
R_1, R_2, R_3, R_4=	H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;
R_5 =	-CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;
R_6 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;
R_7 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocydic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group,
alone or in association with one another or with other natural, semisynthetic, synthetic polymers and, optionally, with biologically active substances, with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

[0016] In yet another aspect, the invention concerns the use of amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R=	NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;
R_1, R_2, R_3, R_4=	H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;
R_5 =	-CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;
R_6 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

R_7 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group

with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond,

either:

for the preparation of salts with pharmacologically active substances;

or:

when alone or in association with one another and/or with pharmacologically active substances for the preparation of pharmaceutical compositions, biomaterials, surgical and health-care articles, slow release systems and systems, for the coating of biomedical objects;

or:

when in association with radioactive and non-radioactive substances, used in contrast systems as labels in in vivo diagnostics, for the identification and treatment of tumoral tissues or damaged tissues.

[0017] These are therefore amides obtained by reaction of an amine with a free carboxyl of hyaluronic acid or a derivative thereof, or by reaction of an acid with a deacylated amino group of hyaluronic acid or a derivative thereof.

[0018] Of the hyaluronic acid derivatives that can be used to prepare amides according to the present invention, the following are preferred:

- hyaluronic acid esters wherein a part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series (EP 0216453 B1);
- autocross-linked esters of hyaluronic acid wherein a part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains (EP 0341745 B1);
- the cross-linked compounds of hyaluronic acid wherein a part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains (EP 0265116 B1);
- hemiesters of succinic acid or the heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid (WO 96/357207);
- the O-sulphated derivatives (WO 95/25751) or N-sulphated derivatives (PCT/EP98/01973).

[0019] Of the amides obtained by reaction of an amine on the carboxyl of hyaluronic acid or of a derivative thereof, of particular interest are the water-soluble ones.

[0020] By amide is meant a group of the formula -CON=.

[0021] Aliphatic means acyclic or pertaining to open-chain or branched carbon compounds such as alkanes, alkenes or alkynes. Examples of an aliphatic moiety include but are not limited to C_1-C_{20} noncyclic hydrocarbons and their isomers such as methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, isobutyl, pentyl, isopentyl, neopentyl, tert-pentyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimcthlbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, cetyl, heptadecyl, octadecyl, nonadecyl, stearyl, etc.

[0022] Aromatic means an aryl moiety having one or more unsaturated rings, each ring usually having 5 to 8 members and preferably 5 to 6 members. Examples of the aromatic moiety include but are not limited to benzyl, toluyl, napthalyl, anthracenyl, phenanthryl, fluorenyl, coronenyl, triphenylenyl, fluoranthenyl, benzofluoranthenyl, benzopyrenyl, and pyrenyl.

[0023] Cycloaliphatic pertains to a carbon ring structure, usually having 3 to 8 members and preferably 5 to 6 members, that does not contain a resonance structure. Examples of cycloaliphatic groups include but are not limited to cycloalkanes and cycloolefins such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclohexenyl (tetrahydrobenzenyl), cyclohexylidenyl, and cyclooctadienyl. The heterocyclic series pertains to disimilar atoms in a ring. A heterocyclic group is a heteroaryl group usually having a 3- to 8-membered, preferably 5- to 6-membered ring or fused ring containing at least one hetero atom (such as O, S, N, etc.) and include but are not limited to thienyl, furanyl, pyranyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, benzothienyl, isobenzofuranyl, chromenyl, indolindinyl, isoindolyl, indolyl, purinyl, quinolidinyl, isoquinolyl, quinolyl, phthalazinyl, quinazolyl, carbazolyl, acridinyl, and phenanthridinyl.

[0024] An arylalkyl group is a group having both aromatic and aliphatic substituents as defined above. Examples of arylalkyl groups include but are not limited to ethylbenzenyl, isobutylbenzeneyl, benzyl, ethylbenzyl, propylbenzyl, isopropylbenzyl, butylbenzyl, isobutylbenzyl, cyclohexylbenzyl, styrenyl, and biphenyl.

[0025] An acyl group is an organic radical derived from an organic acid by the removal of a hydroxy group. Examples

of acyl groups include but are not limited to formyl, acetyl, proprionayl, butyryl, valeryl, isovaleryl, pivaloyl; aroyl such as benzenesufonyl, benzoyl, toluoyl, and napthoyl; diacyl groups such oxalyl and succinic anhydride; and heteroaroyls such as furoyl, nicotnoyl, isonicotinoyl, etc.

[0026] Such amides can be advantageously used for the preparation of pharmaceutical compositions, for example in the form of gels, for the transport and release of drugs or biologically active substances for use in viscoelastic surgery or in ophthalmic surgery.

[0027] The amides according to the present invention can be salified with the heavy metals on the free or sulfuric carboxy groups, meaning by heavy metals the elements of the 4th, 5th and 6th periods of the periodical table such as silver, iron, cobalt, copper, zinc, arsenic, strontium, zirconium, antimony, gold, cesium, tungsten, selenium, platinum, ruthenium, bismuth, tin, titanium and mercury. Said salts can be used in dermatology, in ophthalmology, in dentistry, stomatology, rheumatology, urology, gynaecology, internal surgery, as food supplements, anti-oxidating, anti-rheumatic, anti-tumoural, anti-inflammatory, analgesic and anti-ulcer agents.

[0028] Moreover, the amide derivatives can be obtained by reaction of carboxyl or deacylated nitrogen of hyaluronic acid or a derivative thereof with an amine or with a pharmacologically active acid respectively, or they may be salified or simply associated with said compounds.

[0029] Of the pharmacologically active substances, the following are preferred: antibiotics, anti-infective, antimicrobial, antiviral, cytostatic, cytotoxic, anti-tumoral, anti-inflammatory and wound healing agents, anaesthetics, analgesics, vasoconstrictors, cholinergic or adrenergic agonists and antagonists, anti-thrombotic, anti-coagulant, haemostatic, fibrinolytic and thrombolytic agents, proteins and their fragments, peptides and polynucleotides.

[0030] Hereafter we report some examples of pharmacologically active substances belonging to the aforesaid classes of drugs:

- antibiotics: amino glucosides, macrolides, tetracycline, peptides such as gentamicin, neomycin, streptomycin, dihydrostreptomycin, kanamycin, amikacin, tobramycin, spectinomycin, erythromycin, olcandomycin, carbomycin, spiramycin, oxytetracycline, rolitetracycline, bacitracin, polymyxin B, gramicidin, colistin, chloramphenicol, lincomycin, vancomycin, novobiocin, ristocetin, clindamycin, amphotericin B, griseofulvin, nostatin and their salts;
- anti-infective agents: diethylcarbamazine, mebendazole, sulfamides such as sulfacetamide, sulfadiazine, sulfisoxazole;
- anti-virals and anti-tumorals: iodoxuridine, adenine, adenine arabinoside, trifluorothymidine, acyclovir, ethyldeoxyuridine, bromovinyldeoxyuridine, 5-iodo-5'-amino-2',5'-dideoxyuridine;
- steroid anti-inflammatory agents: dexamethasone, hydrocortisone, prednisolone, fluorometholone, medrisone and their esters;
- non-steroid anti-inflammatory agents: indomethacin, oxyphenbutazone, fluorbiprofene, dichlofenac, ibuprofen;
- anaesthetics: benoxinate, proparacaine, dibucaine, lidocaine, benzocaine, benzydamine, bupivacaine and their salts;
- cholinergic agonists: pilocarpine, methacholine, carbamylcholine, aceclidine, physostigmine, neostigmine, demecarium and their salts;
- cholinergic antagonists: atropine and its salts;
- adrenergic agonists: noradrenalin, adrenalin, naphazoline, methoxamine and their salts;
- adrenergic antagonists: propanol timolol, pindolol, bupranolol, athenolol, methoprolol, oxprenolol, practolol, butoxamine, sotalol, butadrinc, labetalol and their salts;
- antibacterials and disinfectants: nitrofurazone, mafenide, chlorhexidine, the derivatives of 8-hydroxyquinoline and their salts;
- cytotoxics: fluorouracil, methotrexate, podophyllin.

[0031] Of particular interest are the forms for the transport and release of the above said substances and of biologically active substances such as proteins and their fragments, peptides, polynucleotides, growth factors, enzymes, vaccines, substances used in the treatment of diseases associated with genetic defects such as those depending on enzymatic hypo- or hyper-activity due to defects of the gene encoding for a given enzyme, deforming diseases and hereditary diseases.

[0032] The amide derivatives according to the present invention, in association with radioactive and non-radioactive substances, used in contrast systems, can be used as markers in *in vivo* diagnostics, for the identification and treatment of tumour tissues or damaged tissues.

[0033] One considerable advantage is represented by the possibility of processing the amide compounds and their salts in different forms of biomaterials such as sponges, films, membranes, threads, tampons, nonwoven fabric, microspheres, nanospheres, gauzes, gels and guide channels. Said biomaterials, used in one or more associated forms, may be constituted by one or more amide derivatives and their salts, optionally in association with other natural, synthetic or semisynthetic polymers, and optionally, with biologically active stubstances.

[0034] Some examples of natural polymers that can be used are collagen, coprecipitates of collagen and glycosaminoglycans, cellulose, polysaccharides in the form of gels such as chitin, chitosan, pectin or pectic acid, agar, agarose, xanthane, gellan, alginic acid or the alginates, polymannans or polyglycans, starch and natural gums.

[0035] Semisynthetic polymers, for example, can be chosen from the group consisting of collagen cross-linked with agents such as aldehydes or precursors of the same, dicarboxylic acids or their halogenides, diamines, derivatives of cellulose, hyaluronic acid, chitin or chitosan, gellan, xanthane, pectin or pectic acid, polyglycans, polymannan, agar, agarose, natural gum or glycosaminoglycans.

[0036] Lastly, examples of synthetic polymers that can be used are polylactic acid, polyglycolic acid or copolymers of the same or their derivatives, polydioxanes, polyphosphazenes, polysulphonic resin, polyurethanes, PTFE.

[0037] The above said biomaterials can be used to advantage in various fields of surgery, such as in internal and osteo-articular surgery, neuro-surgery, anastomotic, viscoelastic, ophthalmic, oncological, plastic and aesthetic, otorhinolaryngological, abdominal and pelvic, urogynaecological, cardiovascular surgery, in the prevention of post-surgical adhesions and hypertrophic scarring.

[0038] Moreover, the amide compounds in association with fibrin, and optionally other biologically active substances, can be used for the preparation of surgical glues.

[0039] The biomaterials according to the present invention can be used not only in the field of surgery but also in haemodyalisis, cardiology, dermatology, ophthalmology, otorhinolaryngology, dentistry, orthopaedics, gynaecology, urology, in extra-corporeal blood circulation and oxygenation, in cosmetics and in angiology.

[0040] Said biomaterials, in their various forms, can be used to advantage as scaffolds on which to grow cells such as mesenchymal cells or mature cells to obtain connective, glandular and nerve tissue.

[0041] These biopolymers can also be used in the processes of coating objects used both in the medical field and in industrial sectors, giving new biological characteristics to the surfaces of the material used as a support.

[0042] Examples of the objects that can be coated are: catheters, guide channels, probes, cardiac valves, soft tissue prostheses, prostheses of animal origin such as cardiac valves from pigs, artificial tendons, bone and cardiovascular prostheses, contact lenses, blood oxygenators, artificial kidneys, hearts, pancreas, and livers, blood bags, syringes, surgical instruments, filtration systems, laboratory instruments, containers for cultures and for the regeneration of cells and tissues, supports for peptides, proteins and antibodies.

[0043] The process of coating the surface of such objects can be performed, for example by the Plasma Coating technique, described in the international patent application by the Applicant, publication No. WO96/24392.

[0044] The process for the preparation of amides on the nitrogen of hyaluronic acid or one of its deacetylated derivatives can be summarised as the following steps:

- deacetylation reaction, for example, by reaction with hydrazine sulphate (J. Riesenfeld, Analy. Bioch. 1990, vol. 188, pp 383-389);
- preparation of the quaternary ammonium salt of the deacetyalted compound such as the tetrabutylammonium salt;
- preparation of the acylating agent in the form of an active ester, for example, of paranitrophenylester of aliphatic, aromatic, arylaliphatic, cycloaliphatic or heterocyclic acid, chosen for the formation of the amide;
- N-acylation reaction between the quaternary ammonium salt of hyaluronic acid or of one of its deacetylated derivatives and the acylating agent.

The compound is analytically characterised by the following methods:

- *analysis of the percentage of free amino groups:*
  the method described by J. Riesenfeld (Analy. Bioch. 1990, vol. 188, pp 383-389);
- *mean molecular weight:*
  this is determined by GPC using a set of Shadex B-803 and B-806 columns, and RI and MALLS equipment;
  IR and UV spectroscopy analysis:
- *TLC analysis.*
  The sample is hydrolysed in a 1mol. solution of sodium hydroxide for 2-4 hours at 70°C and then acidified with a 1 mol. solution of hydrochloric acid. The acid that is released during hydrolysis is extracted with organic solvent. The dry organic extract is analysed by HPLC.
- *% of N-acylation (hydrolysis of the amide)*
  two types of analysis arc performed to measure the percentate of N-acylated groups:

  a) the method described by J. Riesenfeld (Analy. Bioch. 1990, vol. 188, pp 383-389);
  b) the sample is hydrolysed in a 1 mol. solution of sodium. hydroxide for 2-4 hours at 70°C and then acidified with a 1 mol. solution of hydrochloric acid. The acid that is released during hydrolysis is extracted with organic solvent. The dry organic extract is analysed by HPLC.

[0045] Preparation of the amides on the carboxyl of hyaluronic acid or a derivative thereof consists in activating the carboxy groups by reaction of the same, in acid form or in the form of quaternary ammonium salt, with an agent such as carbonyldiimidazole, which converts carboxylic acid in the reactive form of an acylating agent.

[0046] Said reaction can be performed by catalysis with hydrochloric acid or acid resin and with an amine of the aliphatic, aromatic, arylaliphatic, cycloaliphatic and heterocyclic series.

[0047] Characterisation of the compounds includes the following methods:

- *IR and UV spectroscopy:*
- *Chromatographic analysis.*

  The sample is hydrolysed in a 1 mol. solution of sodium hydroxide for 2-4 hours at 70°C and the amine that is released during hydrolysis ise xtracted with organic solvent. The dry organic extract is analysed by HPLC.

[0048] The percentage of amidation of the product is generally in the range of about 1% to about 90%, more preferably in the range of about 5% to about 60%, and most preferably in the range of about 20% to about 50%.

Example 1

Preparation of partially N-deacetylated hyaluronic acid in the form of sodium salt (DHA/Na)

[0049] One gram of sodium hyaluronate, with a mean molecular weight of 600 Kda, is solubilised in 50 ml of a 1% solution of hydrazine sulphate in hydrazine monohydrate.

[0050] This is left to react under agitation for five days (120 hours) at 55°C, after which the reaction is stopped by adding 100 ml of ethanol.

[0051] The precipitate thus formed is filtered through a Gooch crucible, washed with ethanol and then dried at room temperature at reduced pressure.

[0052] Any hydrazide of hyaluronic acid that will probably be formed during the reaction with hydrazinolysis is destroyed by reaction with HIO_3 (iodic acid). As the reaction may be very vigorous, it is conducted while cooling the reaction container in iced water.

[0053] The product of hydrazinolysis is solubilised in 50 ml of a solution of 5% sodium acetate and reacted with 25 ml of a 0.5 M solution of iodic acid.

[0054] The reaction proceeds for 30 minutes under agitation, after which 5 ml of a 57% solution of HI is added to destroy any unreacted HIO_3.

[0055] The iodine that has formed is extracted from the aqueous solution with at least three 30-ml aliquots of ethyl ether (until complete decolouring of the aqueous phase). The aqueous solution is brought to neutral pH by adding a solution of NaOH 0.5M followed by treatment with 100 ml of ethanol. The precipitate obtained is filtered with a Gooch crucible, washed with ethanol and then dried at room temperature and at reduced pressure.

[0056] The product obtained is characterised analytically to determine the percentage of N-deacetylated groups and the mean molecular weight.

Yield of the reaction	90%
% of N-deacetylation	26%
mean molecular weight	130 Kda

Example 2

Preparation of the salt of hyaluronic acid partially N-deacetylated with tetrabutylammonium (DHA/TBA).

[0057] One gram (2.5 mmol.) of hyaluronic acid sodium salt, partially N-deacetylated, is solubilised in 60 ml of water and the solution is percolated through a column filled with 25 ml of a sulphonic resin in the form of tetrabutylammonium salt (TBA). The sulphonic resin in H^+ form is activated with a 40% solution w/v of TBAOH.

[0058] The eluate, containing N-deacetylated hyaluronic acid TBA salt is collected and freeze-dried.

Example 3

Preparation of p-NO_2-phenylester of benzoic acid (acylating agent)

[0059] Ten grams (0.082 mol.) of benzoic acid is solubilised in 800 ml of CH_2Cl_2, after which 11.4 g (0.082 mol.) of

p-NO_2-phenol and 16.9 g (0.082 mol) of DCC (Dicyclohexylcarbodiimide) are added. The reaction proceeds for 2 hours, while the solution is boiled and refluxed.

[0060] Subsequently, the dicyclohexylurea that forms is filtered and the filtered product is dried with a rotavapor under reduced pressure. The product thus obtained is purified by repeated crystallisation in ethyl acetate. The crystals are filtered and placed to dry at room temperature at reduced pressure.

[0061] The derivative is characterised by TLC analysis (eluent: CH_2Cl_2/ethyl acetate 90/10 and Rf=0.77) and by IR and UV spectroscopy.

Yield of the reaction	92%

Example 4

Preparation of p-NO_2-phenylester of cinnamic acid (acylating agent)

[0062] Twelve grams (0.082 mol.) of cinnamic acid is solubilised in 800 ml of CH2Cl2, after which 11.4 g (0.082 mol.) of p-NO_2-phenol and 16.9 g (0.082 mol) of DCC (Dicyclohexylcarbodiimide) are added. The reaction proceeds for 2 hours during which time the solution is boiled and refluxed.

[0063] Subsequently, the dicyclohexylurea is filtered and the filtered product is dried using a rotavapor at reduced pressure. The product obtained is purified by repeated crystallisation in ethanol, the crystals are filtered and left to dry at room temperature and reduced pressure.

[0064] The derivative is characterised by TLC analysis (eluent: CH_2Cl_2/ethyl acetate 90/10 and Rf=0.77) and by IR and UV spectroscopy.

Yield of the reaction	89%

Example 5

Preparation of p-NO_2-phenylester of dodecanoic acid (acylating agent)

[0065] Sixteen grams of dodecanoic acid is solubilised in 1 litre of CH_2Cl_2, after which 11.4 g (0.082 mol.) of p-NO_2-phenol and 16.9 g (0.082 mol.) of DCC (Dicyclohexylcarbodiimide) are added. The reaction proceeds for 2 hours during which time the solution is boiled and refluxed.

[0066] Subsequently, the dicyclohexylurea is filtered and the filtered product is dried using a rotavapor at reduced pressure. The product obtained is purified by repeated crystallisation in ethyl acetate, the crystals are filtered and left to dry at room temperature and at reduced pressure.

[0067] The derivative is characterised by TLC analysis (eluent: CH_2Cl_2/ethyl acetate 90/10 and Rf = 0.77) and by IR spectroscopy.

Yield of the reaction	93%

Example 6

Preparation of p-NO_2-phenylester of stearic acid (acylating agent)

[0068] 23.3 grams of stearic acid is solubilised in 1 litre of CH_2Cl_2, after which 11.4 g (0.082 mol.) of p-NO_2-phenol and 16.9 g (0.082 mol.) of DCC (Dicyclohexylcarbodiimide) are added. The reaction proceeds for 2 hours during which time the solution is boiled and refluxed.

[0069] Subsequently the dicyclohexylurea is filtered and the filtered product is dried using a rotavapor at reduced pressure. The product obtained is purified by repeated crystallisation in absolute ethanol, the crystals are filtered and left to dry at room temperature at reduced pressure.

[0070] The derivative is characterised by TLC analysis (eluent: CH_2Cl_2/ethyl acetate 90/10 and Rf = 0.82) and by IR spectroscopy.

Yield of the reaction	87%

Example 7

Preparation of p-NO_2-phenylester of o-acetyl salicylic acid (acylating agent)

[0071] 14.7 g of acetylsalicylic acid is solubilised in 1 litre of CH_2Cl_2, after which 11.4 g (0.082 mol.) of p-NO_2-phenol and 16.9 g (0.082 mol.) of DCC (Dicyclohexylcarbodiimide) are added. The reaction proceeds for 2 hours during which time the solution is boiled and refluxed.

[0072] Subsequently, the dicyclohexylurea that forms is filtered and the filtered product is dried using a rotavapor at reduced pressure. The product obtained is purified by repeated crystallisation in absolute ethanol, the crystals are filtered and left to dry at room temperature at reduced pressure.

[0073] The derivative is characterised by TLC analysis (eluent: CH_2Cl_2/ethyl acetate 90/10 and Rf-0.82) and by IR spectroscopy.

Yield of the reaction	80%

Example 8

Preparation of partially N-acylated hyaluronic acid (with the benzoic acid derivative)

[0074] One gram (1.6 mmol.) of DHA/TBA (26% deacetylation) is solubilised in 50 ml of DMSO, after which 5 ml of a 10% solution of p-NO_2-phenylester of benzoic acid (prepared according to example 3) in DMSO is added. The reaction proceeds for 24 hours, under agitation at room temperature, after which it is blocked by adding 2.5 ml of a saturated solution of NaCl. This is left to react for 30 minutes and then 100 ml of ethanol is slowly added. The precipitate thus obtained is filtered through a Gooch, washed with ethanol and ethyl ether and lastly dried at room temperature and at reduced pressure.

[0075] The derivative is analysed by TLC (after hydrolysis of the amide), colorimetric analysis of the percentage of free NH_2 groups and IR and UV spectroscopy.

Yield of the reaction	85%
% free NH_2	11 %
% N-acylation	15%

Example 9

Preparation of partially N-acylated hyaluronic acid (with the derivative of cinnamic acid)

[0076] One gram (1.6 mmol.) of DHA/TBA (26% deacteylation) is solubilised in 50ml of NMP, after which 10 ml of a 10% solution of p-NO_2-phenylester of cinnamic acid (prepared according to example 4) in NMP is added. The reaction proceeds for 24 hours, under agitation, at room temperature, after which it is blocked by adding 2.5 ml of a solution saturated with NaCl. This is left to react for 30 minutes and lastly 100 ml of ethanol is slowly added. The precipitate thus obtained is filtered through a Gooch crucible, washed with ethanol/water 9:1, ethyl ether and lastly dried at room temperature at reduced pressure.

[0077] The derivative is analysed by TLC (after hydrolysis of the amide), colorimetric analysis of the percentage of free NH_2 groups and IR and UV spectroscopic analysis.

Yield of the reaction	85%
% free NH_2	11%
% N-acylation	15%

Example 10

Preparation of partially N-acylated hyaluronic acid (with a derivative of dodecanoic acid)

[0078] One gram (1.6 mmol.) of DHA/TBA (26% deacetylation) is solubilised in 50 ml of NMP, after which 3.2 ml of a 10% solution of p-NO_2-phenylester of dodecanoic acid (prepared according to example 5) in NMP is added. The reaction proceeds for 24 hours, under agitation, at room temperature, after which it is blocked by adding 2.5 ml of a

saturated solution of NaCl. This is left to react for 30 minutes, after which 100 ml of ethanol is gently added. The precipitate obtained is filtered through a Gooch , washed with ethanol and ethyl ether and lastly dried at room temperature at reduced pressure.

[0079] The derivative is analysed by TLC (after hydrolysis of the amide), colorimetric analysis of the percentage of free NH_2 groups and IR and UV spectroscopy.

Yield of the reaction	88%
% freeNH_2	10%
% N-acylation	16%

Example 11

Preparation of partially N-acylated hyaluronic acid (with the derivative of stearic acid)

[0080] One gram (1.6 mmol) of DHA/TBA (26% deacetylation) is solubilised in 50 ml of NMP, after which 6 ml of a 10% solution of p-NO_2-phenylester of stearic acid (prepared according to example 6) in NMP is added. The reaction proceeds for 24 hours under agitation at room temperature after which it is blocked by adding 2.5 ml of a saturated solution of NaCl. This is left to react for 30 minutes and then 100 ml of ethanol is slowly added. The precipitate thus obtained is filtered through a Gooch filter, washed with ethanol and ethyl ether and lastly left to dry at room temperature and reduced pressure.

[0081] The derivative is analysed by TLC (after hydrolysis of the amide), colorimetric analysis of the percentage of free NH_2 groups and IR and UV spectroscopy.

Yield of the reaction	85%
% free NH_2	12%
% N-acylation	14%

[0082] IR spectroscopy (Figure 1): the figure shows the difference between the IR spectrum of the amide and that of hyaluronic acid sodium salt. In the spectrum of the amide, there is an evident peak in the area of 2900 cm-1, due to the stretching of the CH_2 of the stearate.

Example 12

Preparation of partially N-acylated hyaluronic acid (with acetyl salicylic acid derivative)

[0083] One gram (1.6 mmol.) of DHA/TBA is solubilised in 50 ml of NMP, after which 3.2 ml of a 10% solution of p-NO_2-phenylester of acetyl salicylic acid (prepared according to example 7) in NMP is added. The reaction proceeds for 24 hours under agitation at room temperature, after which it is blocked by adding 2.5 ml of a saturated solution of NaCl. This is left to react for 30 minutes and lastly 100 ml of ethanol is slowly added. The precipitate thus obtained is filtered through a Gooch crucible, washed with ethanol and ethyl ether and then dried at room temperature and reduced pressure.

[0084] The derivative is analysed by TLC (after hydrolysis of the amide), colorimetric analysis of the percentage of free NH_2 groups and IR and UV spectroscopy.

Yield of the reaction	90%
% free NH_2	10%
% N-acylation	16%

Example 13

Preparation of benzylamide of hyaluronic acid

[0085] Two grams (3.2 mmol.) of tetrabutylammonium salt of hyaluronic acid (HA/TBA) is solubilised in 100 ml of DMSO. This solution is supplemented with 3 ml of humid acid resin in DMSO and 784 mg (4.8 mmol.) of 1,1-carbonyldiimidazole. This is left to react under agitation for 12 hours, after which it if filtered through a Gooch crucible to eliminate the resin and the filtered product is supplemented with 1 ml (9.6 mmol) of benzylamine. This is left to react

for 48 hours and then 5 ml of a saturated solution of NaCl is added and it is left under agitation for 30 minutes. It is supplemented with 200 ml of acetone and the precipitate thus obtained is filtered and dried at reduced pressure. The dry derivative is characterised by TLC, IR and HPLC analysis.

% of amidation	25%

[0086] IR spectroscopy (Figures 2 and 3): the spectrum in figure 2 clearly shows a peak at 1537 cm-1 due to bending in the NH plane (the amide band) and a peak at about 730 cm-1 due to bending of the CH outside the plane of the aromatic ring. Figure 3 shows the difference between the graph relative to the amide and that of the sodium salt of hyaluronic acid.

Example 14

Preparation of benzylamide of hyaluronic acid

[0087] Two grams (3.2 mmol.) of tetrabutylammonium salt of hyaluronic acid (HA/TBA) is solubilised in 100 ml of DMSO. The solution is adjusted to pH 3 with HCl 1M and then 784 mg (4.8 mmol.) of 1,1-carbonyldiimidazole is added. This is left to react under agitation for 12 hours, then it is filtered through a Gooch crucible to eliminate the resin and 1 ml (9.6 mmol.) of benzylamine is added to the filtered product. This is left to react for 48 hours, then 5 ml of a saturated solution of NaCl is added and left under agitation for 30 minutes. To this is added 200 ml of acetone, the precipitate thus obtained is filtered and dried under reduced pressure.

[0088] The dry derivative is characterised by TLC, IR and HPLC analysis.

% amidation	15%

Example 15

Preparation of benzylamide of hyaluronic acid

[0089] Two grams (5.2 mmol.) of hyaluronic acid in acid form is solubilised in 100 ml of DMF. To this solution is added 854 mg (5.2 mmol.) of 1,1-carbonyldiimidazole. This is left to react under agitation for 6 hours, after which 1.13 ml (10.4 mmol.) of benzylamine is added. The reaction proceeds for 48 hours, and is then blocked by adding 200 ml of acetone. The precipitate thus obtained is filtered and dried under reduced pressure.

[0090] The dry derivative is characterised by TLC, TR and HPLC analysis.

% amidation	60%

Example 16

Preparation of benzylamide of hyaluronic acid

[0091] Two grams (5.2 mmol.) of hyaluronic acid in acid form is solubilised in 100 ml of DMF. To this solution is added 2 ml of pyridine, 3.68 g (0.026 mol.) of p-NO_2-phenol and pyridine chloride until a pH of 7/8 is reached. Lastly, 5.3 (0.026 mol.) of DCC and 2.8 (0.026 mol.) of benzylamine are added. This is left to react under agitation for 16 hours after which the reaction is blocked by adding 200 ml of acetone. The precipitate thus obtained is filtered and dried under reduced pressure.

[0092] The dry derivative is characterised by TLC, IR and HPLC analysis.

% amidation	5%

Example 17

Preparation of benzylamide of hyaluronic acid

[0093] Two grams (3.2 mmol.) of HA/TBA is solubilised in 100 ml of DMSO. The solution is insufflated with gaseous HCl until the reaction mixture reaches a pH of between 4.5 and 5. Subsequently, 518 mg (3.2 mmol.) of carbonyldiim-

idazole is added. It is left to react under agitation for one hour at room temperature, after which 0.700 ml (6.4 mmol.) of benzylamine is added. The reaction proceeds for 16-18 hours. After this time, 5 ml of a solution saturated with NaCl is added. It is precipitated by adding 200 ml of acetone and the precipitate thus obtained is filtered and dried under reduced pressure.

[0094] The dry derivative is characterised by TLC (after hydrolysis), IR and HPLC analysis.

% amidation	50%

Example 18

Preparation of the octylamide of hyaluronic acid

[0095] Two grams (3.2 mmol.) of HA/TBA is solubilised in 100 ml of DMSO. The solution is insufflated with gaseous HCl till the reaction mixture reaches a pH of between 4.5 and 5. Subsequently, 207 mg (1.28 mmol.) of carbonyldiimidazole is added. It is left to react under agitation for one hour at room temperature, after which 0.417 ml (3.2 mmol.) of octylamine is added. The reaction proceeds for 16-18 hours. At the end of this time, 5 ml of a solution saturated with NaCl is added. It is precipitated by adding 200 ml of acetone and the precipitate obtained is filtered and dried under reduced pressure.

[0096] The dry derivative is characterised by TLC (after hydrolysis), IR and HPLC analysis.

% amidation	25%

Example 19

Preparation of the dodecyl amide of hyaluronic acid:

[0097] Two grams (3.2 mmol.) of HA/TBA is solubilised in 100 ml of DMSO. The solution is insufflated with gaseous HCl till the reaction mixture reaches a pH of between 4.5 and 5. Subsequently, 104 mg (0.64 mmol.) of carbonyldiimidazole is added. It is left to react, under agitation, for one hour at room temperature, after which 600 mg (3.2 mmol.) of dodecylamine is added. The reaction proceeds for 16-18 hours. After this time, 5 ml of a solution saturated with NaCl is added. It is precipitated by adding 200 ml of acetone and the precipitate obtained is filtered and dried under reduced pressure.

[0098] The dry derivative is characterised by TLC (after hydrolysis), IR and HPLC analysis.

% amidation	15%

Example 20

Preparation of the hexadecylamide of hyaluronic acid:

[0099] Two grams (3.2 mmol.) of HA/TBA is solubilised in 100 ml of DMSO. The solution is insufflated with gaseous HCl till the reaction mixture reaches a pH of between 4.5 and 5. Subsequently, 52 mg (0.32 mmol.) of carbonyldiimidazole is added and left to react under agitation for one hour at room temperature, after which 780 mg (3.2 mmol.) of hexadecylamine is added. The reaction proceeds for 16-18 hours. After this time, 5 ml of a solution saturated with NaCl is added. It is precipitated by adding 200 ml of acetone and the precipitate obtained is filtered and dried under reduced pressure.

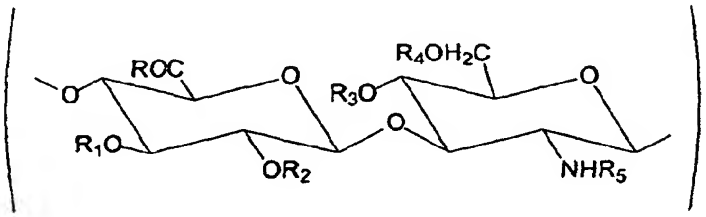
[0100] The dry derivative is characterised by TLC (after hydrolysis), IR and HPLC analysis.

% amidation	5%

[0101] The invention being thus described, it is clear that these methods can be modified in various ways. Such modifications are not to be considered as divergences from the spirit and purpose of the invention and any modification that would appear evident to an expert in the field comes within the scope of the following claims:

Claims

1. Amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R=	NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;
R_1, R_2, R_3, R_4 =	H, SO_3^-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, $-CO-(CH_2)_2-COOY$; Y = negative charge, or H;
R_5 =	$-CO-CH_3$, H, SO_3^-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;
R_6 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;
R_7 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group,
with the provisos that when R_6 is H, R_7 is not $-CH_2CO_2CH_3$, and that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

2. Amidic, water-soluble compounds of claim 1 obtained by reaction of the carboxylic groups of hyaluronic acid with an amino group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series for use in ophthalmology and in ophthalmic surgery.

3. Amidic compounds according to claim 1, wherein the hyaluronic acid derivatives are total or partial esters with aliphatic, aromatic, arylaliphatic, cycloaliphatic, heteroaliphatic alcohols.

4. Amidic compounds according to claim 1, wherein the hyaluronic acid derivatives are cross-linked compounds wherein part or all of the carboxy groups of the D-glucuronic residue form inner or inter-molecular esters with the alcoholic functions of the same polysaccharide chain or other chains respectively.

5. Amidic compounds according to claim 1, wherein the hyaluronic acid derivatives are cross-linked compounds wherein a part or all of the carboxy groups of the D-glucuronic residue are made to react with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains.

6. Amidic compounds according to claim 1, salified with heavy metals.

7. Amidic compounds according to claim 6, wherein the heavy metals are those of the 4^{th}, 5^{th} and 6^{th} group of the table of elements and preferably silver, cobalt, iron, copper, zinc, arsenic, strontium, zirconium, antimony, gold, cesium, tungsten, selenium, platinum, ruthenium, bismuth, tin, titanium and mercury.

8. Amidic compounds according to claims 1-7, salified with pharmacologically active substances.

9. Amidic compounds according to claim 8, wherein the pharmacologically active substances are antibiotics, anti-

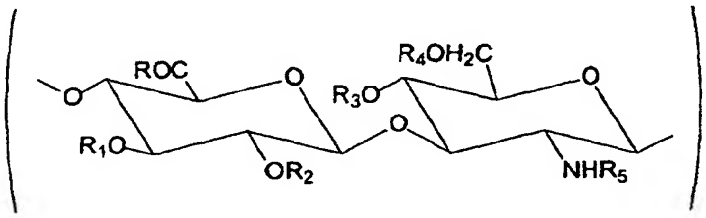
infective, antimicrobial, antiviral, cytostatic, antitumoral, anti-inflammatory, wound heating agents, anaesthetics, cholinergic or adrenergic agonists and antagonists, antithrombotic, anticoagulant, haemostatic, fibrinolytic, thrombolytic agents, proteins and their fragments, peptides, polynucleotides.

10. Amidic compounds and their salts according to claims 1-9, alone or in association with one another and/or with pharmacologically active substances for the preparation of pharmaceutical compositions.

11. Amidic compounds and their salts according to claim 10, wherein the pharmacologically active substances are antibiotics, anti-infective, antimicrobial, antiviral, cytostatic, antitumoral, anti-inflammatory, wound healing, anaesthetic agents, cholinergic or adrenergic agonists or antagonists, antithrombotic, anticoagulant, haemostatic, fibrinolytic, thrombolytic agents, proteins and their fragments, peptides, polynucletotides, growth factors, enzymes, vaccines, substances used in the treatment of dieases associated with genetic defects, deforming diseases and hereditary diseases.

12. Amidic compounds according to the previous claims, in association with radioactive or non-radioactive substances, used in contrast systems as labels in in vivo diagnostics to identify and treat tumoral tissues or damaged tissues.

13. Pharmaceutical compositions containing
amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:

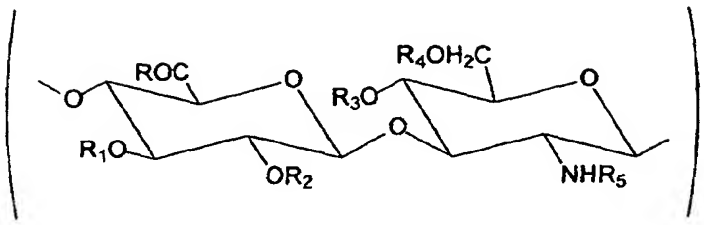


wherein:

R =	NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;
R_1, R_2, R_3, R_4=	H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;
R_5 =	-CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;
R_6 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;
R_7 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group,
alone or in association with one another or with other pharmacologically active substances and in association with a pharmaceutically acceptable carrier, with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

14. Biomaterials constituted by amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R=	NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloallphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;
R_1, R_2, R_3, R_4=	H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;
R_5 =	-CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;
R_6 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;
R_7 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group,
alone or in association with one another or with other natural, semisynthetic, synthetic polymers and, optionally, with biologically active substances, with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

15. Biomaterials according to claim 14, wherein the natural polymers are collagen, coprecipitates of collagen and glycosaminoglycans, cellulose, polysaccharides in the form of gels such as chitin, chitosan, pectin or pectic acid, agar, agarose, xanthane, gellan, alginic acid or alginates, polymannans or polyglycans, starch, natural gums.

16. Biomaterials according to claim 14, wherein the semisynthetic polymers are collagen cross-linked with agents such as aldehydes or precursors of the same, dicarboxylic acids or their halogenides, diamines, derivatives of cellulose, hyaluronic acid, chitin or chitosan, gellan, xanthane, pectin or pectic acid, polyglycans, polymannan, agar, agarose, natural gum or glycosaminoglycans.

17. Biomaterials according to claim 14, wherein the synthetic polymers are polylactic acid, polyglycolic acid or copolymers of the same or their derivatives, polydioxanes, polyphosphazenes, polysulphonic resins, polyurethanes, PTFE.

18. Biomaterials according to claims 14-17, in association with fibrin, and optionally with other biologically active substances for the preparation of surgical glues.

19. Biomaterials according to claims 14-17 for the preparation of scaffolds for cell cultures.

20. Biomaterials according to claims 14-17 for the preparation of surgical and health-care articles.

21. Biomaterials according to claims 14-17, in the form of guide channels, gauzes, threads, gels, hydrogels, tampons, films, membranes, sponges, non-woven fabrics, microspheres, nanospheres and associations of the same.

22. Surgical and health-care articles according to claim 20, in the form of guide channels, gauzes, threads, gels, hydrogels, tampons, films, membranes, sponges, non-woven fabrics, microspheres, nanospheres.

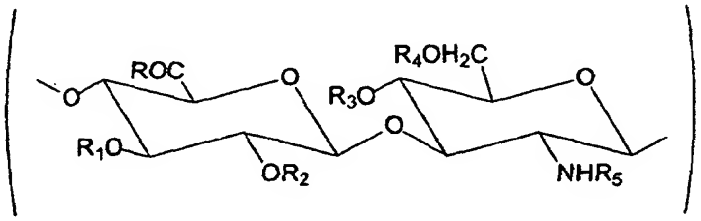
23. Biomaterials according to claims 14-17 for use in surgery, haemodialysis, cardiology, dermatology, ophthalmology, ororhinolaryngology, dentistry, orthopaedics, gynaecology, urology, in extra-corporeal blood circulation and oxygenation, in cosmetics, in angiology.

24. Biomaterials according to claim 23 where surgery should be taken to mean internal or osteoarticular surgery, neurosurgery, anastomotic, viscoelastic, ophthalmic, oncological, plastic, aesthetic, otorhinolaryngological, abdominal-pelvic, urogynaecological or cardiovascular surgery, such as in the preparation of cardiac valves, vascular stents, in the prevention of post-surgical adhesions and hypertrophic scarring.

25. Amidic compounds and their salts according to claims 1-9 for the coating of biomedical objects such as bypasses, venous catheters, shunts, catheters, guide channels, probes, cardiac valves, artificial tendons, bone and cardiovascular prostheses, contact lenses, soft tissue prostheses, prostheses of animal origin, blood oxygenators, artificial kidneys, hearts, pancreas and livers, blood bags, syringes, surgical instruments, filtration systems, laboratory instruments, containers for cell cultures and for the regeneration of cells and tissues, supports for peptides, proteins, antibodies.

26. Use of the amidic compounds according to claims 7-8, in dermatology, ophthalmology, dentistry, stomatology, rheumatology, urology, gynaecology, internal surgery, as food supplements, anti-oxidant, anti-rheumatic, anti-tumoral, anti-inflammatory, analgesic, anti-ulcer agents.

27. Use of amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:

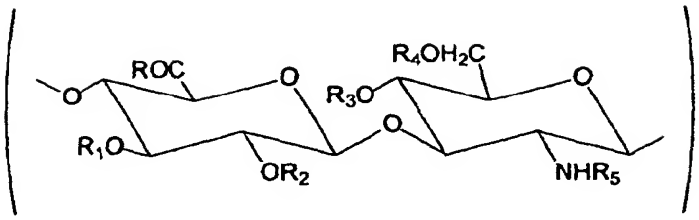


wherein:

R =	NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;
R_1, R_2, R_3, R_4 =	H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;
R_5 =	-CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;
R_6 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;
R_7 =	is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group
with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond,
for the preparation of salts with pharmacologically active substances.

28. Use of amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R= NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;

R_1, R_2, R_3, R_4= H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;

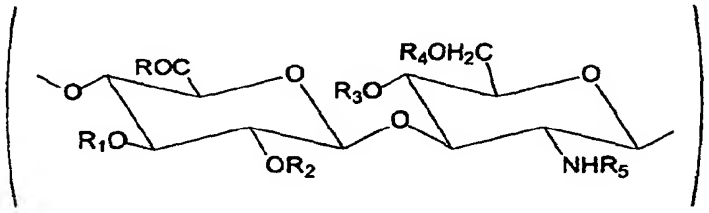
R_5 = -CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;

R_6 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

R_7 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group alone or in association with one another and/or with pharmacologically active substances for the preparation of pharmaceutical compositions, biomaterials, surgical and health-care articles, slow release systems and systems for the coating of biomedical objects, with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

29. Use of amidic water-soluble compounds of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R= NR_6R_7, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;

R_1, R_2, R_3, R_4 = H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO-$(CH_2)_2$-COOY; Y = negative charge, or H;

R_5 = -CO-CH_3, H, SO_3-, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;

R_6 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

R_7 = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R_5 forms an amide group in association with radioactive and non-radioactive substances, used in contrast systems as labels in in vivo diagnostics for the identification and treatment of tumoral

tissues or damaged tissues, with the proviso that the amidic, water-soluble compound is not combined with a medicinal ingredient through an amide bond.

30. Use of the amidic compounds and their salts according to claim 28, wherein the biomaterials are in the form of guide channels, gauzes, threads, gels, hydrogels, tampons, films, membranes, sponges, non-woven fabrics, microspheres, nanospheres and associations of the same.

31. Use of the amidic compound according to the previous claims, in surgery, haemodialysis, cardiology, dermatology, ophthalmology, otorhinolaryngology, dentistry, orthopaedics, gynaecology, urology, in extracorporeal blood circulation and oxygenation, in cosmetics and in angiology.

32. Use of the amide compounds according to claim 31, where surgery means internal, osteo-articular surgery, neurosurgery, anastomotic, viscoelastic, ophthalmic, oncological, plastic aesthetic, otorhinolaryngological, abdominal pelvic, urogynaecological, cardiovascular surgery such as in the preparation of cardiac valves, vascular stents, in the prevention of post-surgical adhesions and in hypertrophic scarring.

33. Use of biomaterials according to claims 14-17, in association with fibrin, and optionally with other biologically active substances for the preparation of surgical glues.

34. Use of biomaterials according to claims 14-17 for the preparation of scaffolds for cell cultures.

35. Process for the preparation of amides on the nitrogen of hyaluronic acid or a deacetylated derivative thereof involving the following steps:

    a) deacetylation reaction;
    b) preparation of the quaternary ammonium salt of the deacetylated compound;
    c) preparation of the acylating agent in the form of active ester;
    d) N-acylation reaction between the quaternary ammonium salt of hyaluronic acid or a deacetylated derivative thereof and the acylating agent.

36. Process according to claim 35, wherein the deacetylation reaction is obtained by using hydrazine sulphate/hydrazine.

37. Process according to claim 35, wherein the quaternary ammonium salt is the tetrabutylammonium salt.

38. Process accirding to claim 35, wherein the active ester is the paranitrophenyl ester of aliphatic, aromatic, arylatiphtic, cycloaliphatic, heterocyclic acid, chosen for the formation of the amide.

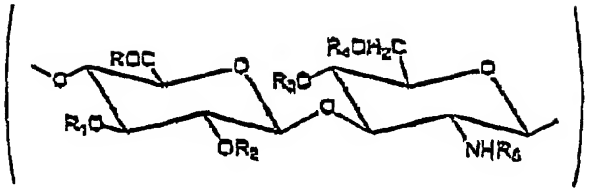
39. Process for the preparation of the amidic, water soluble compounds of claim 1 having the amides on the carboxyl of hyaluronic acid or a derivative thereof, involving the following steps:

    a) activation of the carboxy groups by reaction of the same, in the acid form or as a quaternary ammonium salt, with an activating agent, in acid solution or on acid resin;
    b) reaction with an amine of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series.

40. Process according to claim 39, wherein the activating agent is 1,1-carbonyldiimidazole.

Patentansprüche

1. Amidische, wasserlösliche verbindungen von Hyaluronsäure oder einem Derivat davon, umfassend wenigstens eine Repetier-einheit der folgenden allgemeinen Formel:



worin:

R = NR_6R_7 oder eine alkoholische Gruppe der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe, OH, O-, alkoholische Hyaluronsäuregruppe, Aminogruppe von deacylierter Hyaluronsäure;

R_1, R_2, R_3, R_4 = H, SO_3-, Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe stammt, -CO- $(CH_2)_2COOY$, Y = negative Ladung oder H;

R_5 = -CO-CH_3, H, SO_3-, Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe stammt, Acylgruppe von Hyaluronsäure,

R_6 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

R_7 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder nicht substituiert ist;

wobei mindestens eines von R und R_5 eine Amidgruppe bildet,
mit den Maßgaben, dass, wenn R_6 H ist, R_7 nicht -$CH_2CO_2CH_3$ ist, und dass die wasserlösliche, amidische Verbindung nicht über eine Amidbindung mit einem medizinischen Ingredienz verbunden ist.

2. Amidische, wasserlösliche Verbindungen nach Anspruch 1, die durch Reaktion der Carboxylgruppe von Hyaluronsäure mit einer Aminogruppe der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe erhalten werden, zur Verwendung in der Ophthalmologie und der Augenchirurgie.

3. Amidische Verbindungen nach Anspruch 1, wobei die Hyaluronsäurederivate vollständige oder Partialester mit aliphatisehen, aromatischen, arylaliphatischen, cycloaliphatischen, heteroaliphatischen Alkoholen sind.

4. Amidische Verbindungen nach Anspruch 1, wobei die Hyaluronsäurederivate vernetzte Verbindungen sind, worin ein Teil der carboxygruppen des D-Glucuronsäurerests oder alle Carboxygruppen das D-Glucuronsäurerests intra- oder intermolekulere Ester mit den alkoholischen Funktionen derselben Polysaccharidkette bzw. anderer Ketten bilden.

5. Amidische Verbindungen nach Anspruch 1, wobei die Hyaluronsäurederivate vernetzte Verbindungen sind, in denen ein Teil der Carboxygruppen des D-Glucuronsäurerests oder alle Carboxygruppen des D-Glucuronsäurerests mit Polyalkoholen der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe umgesetzt wurden, wodurch eine Vernetzung mittels Spacerketten erzeugt wurde.

6. Amidische Verbindungen nach Anspruch 1, die ein Salz mit Schwermetallen gebildet haben.

7. Amidische Verbindungen nach Anspruch 6, wobei die Schwermetalle solche der vierten, fünften und sechsten Gruppe des Periodensystems und vorzugsweise Silber, Kobalt, Eisen, Kupfer, Zink, Arsen, Strontium, Zirkonium, Antimon, Gold, Caesium, Wolfram, Selen, Platin, Ruthenium, Wismut, Zinn, Titan und Quecksilber sind.

8. Amidische Verbindungen nach den Ansprüchen 1 bis 7, die mit pharmakologisch aktiven Substanzen ein Salz gebildet haben.

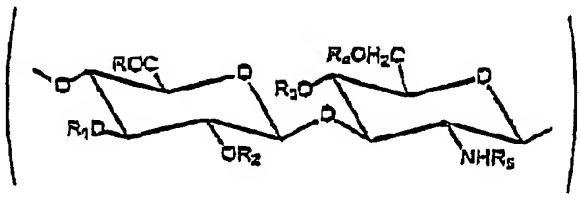
9. Amidische Verbindungen nach Anspruch 8, wobei die biologisch aktiven Substanzen Antibiotika, Antiinfektiosa, antimikrobielle Mittel, antivirale Mittel, Cytostatika, Antitumormittel, antiinflammatorische Mittel, Wundheilungsmittel, Narkotika, cholinerge oder adrenerge Agonisten und Antagonisten, Mittel gegen Thrombose, Antikoagulantien, Hämostatika, fibrinolytische, thrombolytische Mittel, Proteine und deren Fragmente, Peptide, Nucleotide sind.

10. Amidische Verbindungen und ihre Salze nach den Ansprüchen 1 bis 9, allein oder in Verbindung miteinander und/oder mit pharmakologisch aktiven Substanzen zur Herstellung von pharmazeutischen Zusammensetzungen.

11. Amidische Verbindungen und ihre Salze nach Anspruch 10, wobei die pharmakologisch aktiven Substanzen Antibiotika, Antiinfektiosa, antimikrobielle Mittel, antivirale Mittel, Cytostatika, Antitumormittel antiinflammatorische mittel, Wundheilungsmittel Narkotika, chelinerge oder adrenerge Agonisten oder Antagonisten, Mittel gegen Thrombose, Antikoagulantien, Hämostatika, fibrinolytische, thrombolytische Mittel, Proteine und ihre Fragmente, Peptide, Polynukleotide, Wachstumsfaktoren, Enzyme, Vakzine, Substanzen, die bei der Behandlung von Krankheiten, assoziiert mit genetischen Defekten, Missbildungserkrankungen und Erbkrankheiten verwendet werden, sind.

12. Amidische Verbindungen nach den vorangehenden Ansprüchen in Verbindung mit radioaktiven oder nicht radioaktiven Substanzen, die in Kontratsystemen als Markierungen bei der in vivo-Diagnostik zur Identifizierung und Behandlung von Tumorgeweben oder geschädigten Geweben verwendet werden.

13. Pharmazeutische Zusammensetzungen, enthaltend amidische, wasserlösliche Verbindungen von Hyaluronsäure oder einem Derivat davon, umfassend wenigstens eine Repetiereinheit der folgenden allgemeinen Formel:



worin:

R = NR_6R_7 oder eine alkoholische Gruppe der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe, OH, O-, eine alkoholische Gruppe von Hyalurönsäure, eine Aminogruppe von deacylierter Hyaluronsäure;

R_1, R_2, R_3, R_4 = H, SO_3-, Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, -CO- $(CH_2)_2$-COOY, Y = negative Ladung oder H;

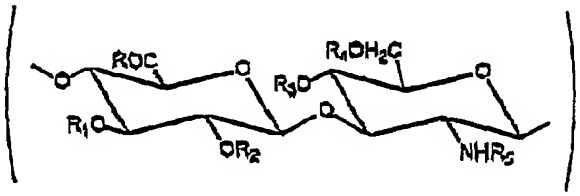
R_5 = -CO-CH_3, H, SO_3-, eine Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, eine acylgruppe von Hyaluronsäure;

R_6 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heteroliphatische, cycloaliphatische oder heterocyclische Gruppe, die substitutiert oder unsubstituiert ist;

R_7 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

wobei wenigstens einer von R und R_5 eine Amidgruppe bildet,
allein oder in Kombinabion Miteinander oder mit anderen pharmakologisch aktiven Substanzen und in Kombination mit einem pharmazeutisch annehmbaren Träger, mit der Maßgabe, dass die amidische, wasserlösliche Verbindung nicht durch eine Amidbindung mit einem medizinischen Ingredienz verbunden ist.

14. Biomaterialien, gebildet durch amidische, wasserlösliche Verbindungen von Hyaluronsäure oder einem Derivat davon, umfassend wenigstens eine Repetiereinheit der folgenden allgemeinen Formel:



worin:

R = NR_6R_7 oder eine alkoholische Gruppe der aliphatisehen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe, OH, O-, eine alkoholische Gruppe von Hyaluronsäure, eine Aminogruppe von deacylierter Hyaluronsäure;

R_1, R_2, R_3, R_4 = H, SO_3-, Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, -CO- $(CH_2)_2$-COOY, Y = negative Ladung oder H;

R_5 = -CO-CH_3, H, SO_3-, eine Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, eine Acylgruppe von Hyalurönsäure;

R_6 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die subsbituiert oder unsubstituiert ist;

R_7 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

wobei wenigstens eine von R und R_5 eine Amidgruppe bildet,
alleine oder in Kombination Miteinander oder mit anderen natürlichen, halbsynthetischen, synthetischen Polymeren und gegebenenfalls mit biologisch aktiven Substanzen, mit der Maßgabe, dass die amidische, wasserlösliche Verbindung nicht durch eine Amidbindung mit einem medizinischen Ingredienz verbunden ist.

15. Biomaterialien nach Anspruch 14, wobei die natürlichen Polymere Kollagen, Co-Präzipitate von Kollagen und Glycosaminoglycanen, Cellulose, Polysaccharide in Form von Galen wie Chitin, Chitosan, Pektin oder Pektinsäure, Agar, Agarose, Xanthan, Gellan, Alginsäure oder Alginate, Polymannane oder Polyglykane, Stärke, Naturgummis sind.

16. Biomaterialien nach Anspruch 14, wobei die halbsynthetischen Polymere Kollagen, vernetzt mit Agenzien wie Aldohyden oder Vorläufern derselben, Dicarbonsäuren oder deren Halogeniden, Diaminen, Cellulosederivate, Hyaluronsäure, Chitin oder Chitosan, Gellan, Xanthan, Pectin oder Pectinsäure, Polyglycane, Polymannan, Agar, Agarose, Naturgummi oder Clycosaminoglycane sind.

17. Biomaterialen nach Anspruch 14, wobei die synthetischen Polymere Polymilchsäure, Polyglycolsäure oder Copolymer derselben oder ihrer Derivate, Polydioxane, Polyphosphazene, Polysulfonsäureharze, Polyurethane, PTFE sind.

18. Biomaterialien nach den Ansprüchen 14 bis 17 in Verbindung mit Fibrin und gegebenenfalls mit anderen biologisch aktiven Substanzen zur Herstellung von chirurgischen Leimen.

19. Biomaterialien nach den Ansprüchen 14 bis 17 zur Herstellung von Gerüsten für Zellkulturen.

20. Biomaterialien nach den Ansprüchen 14 bis 17 zur Herstellung von chirurgischen Gegenständen und Gegenständen für die Gesündheitsfürsorge.

21. Biomaterialien nach den Ansprüchen 14 bis 17 in Form von Führungskanälen, Gaze, Fäden, Gelen, Hydrogelen, Tampons, Filmen, Membranen, Schwämmen, Faservliesen, Mikrokügelchen, Nanokügelchen und Kombinationen derselben.

22. Chirurgische Gegenstände und Gegenstände zur Besundheitsfürsorge nach Anspruch 20 in Form von Führungskanälen, Gaze, Fäden, Gelen, Hydrogelen, Tampons, Filmen, Membranen, Schwämmen, Faservliesen, Mikrokügelchen, Nanokügelchen.

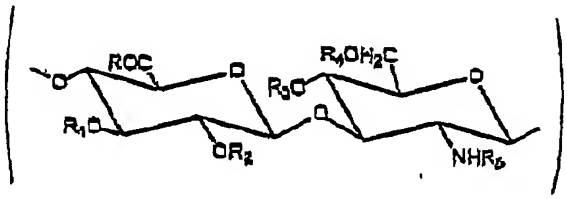
23. Biomaterialien nach den Ansprüchen 14 bis 17 zur Verwendung in der Chirurgie, Hämodialyse, Kardiologie, Dermatologie, Ophthalmologie, Otorhinolaryngologie, Zahnheilkunde, Orthopädie, Gynäkologie, Urologie, beim extrakorporalen Blutkreislauf und der extrakorporalen Oxygenation, in der Kosmetik und der Angiologie.

24. Biomaterialien nach Anspruch 23, wobei Chirurgie bezeichnen soll: innere und osteoartikuläre Chirurgie, Neurochirurgie, Anastomosenchirurgie, viskoelastische, ophthalmische, onkologische, plastische, ästhetische; otorinolaryngologische Chirurgie, Abdomen-Becken-Chirurgie, urogynäkologische oder kardiovaskuläre Chirurgie, zum Beispiel bei, der Herstellung von Herzklappen, Gefaßstents, bei der Prävention von Adhäsionen nach Operation und der hypertrophen Vernarbung.

25. Amidische Verbindungen und ihre salze nach den Ansprüchen 1 bis 9 für die Beschiehtung biomedizinischer Objekte wie Bypässe, Venenkatheter, Shunts, Katheter, Führungskanäle, Sonden, Merzklappen, künstliche Sehnen, Knochen- und kardiovaskuläre Prothesen, Kontaktlinsen, Bindegewebsprothesen, Prothesen tierischen Ursprungs, Blutoxygenatoren, künstliche Nieren, Herzen, Pankreas und Leber, Blutbeutel, Spritzen, chirurgische Instrumente, Filtrationssysteme, Laborinstrumente, Behälter für Zellkulturen und für die Regeneration von Zellen und Geweben, Träger für Peptide, Proteine, Antikörper.

26. Verwendung der amidischen Verbindungen nach den Ansprüchen 7 bis 8 in der Dermatologie, Ophthalmologie, Zahnheilkunds, Stomatologie, Rheumatologie, Urologie, Gynäkologie, inneren Chirurgie, als Nahrungsmittelergänzungen, Antioxidanz, Antirheumatikum, Antitumormittel, antiinflammatorisches Mittel, Analgetikum, Mittel gegen Ulcus.

27. Verwendung von amidischen, wasserlöslichen Verbindungen von Hyaluronsäure oder einem Derivat davon, umfassend die wenigstens eine Repetiezeinheit der folgenden allgemeinen Formel:



worin:

R = NR_6R_7 oder eine alkoholische Gruppe der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe, OH, O-, eine alkoholische Gruppe von Hyaluronsäure, eine Aminogruppe von deacylierter Hyaluronsäure;

R_1, R_2, R_3, R_4 = H, SO_3-, Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyctischen Reihe abgeleitet ist, -CO- $(CH_2)_2$-COOY, Y = negative Ladung oder H;

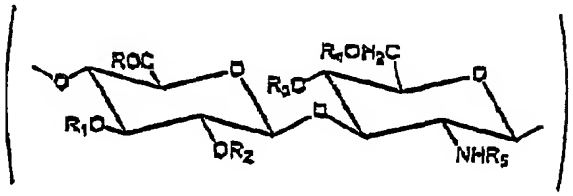
R_5 = -CO-CH_3, H, SO_3-, eine Acylgruppe, die von einer Carbonsäure der aliphatischen, aramatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, eine Acylgruppe von Myaluronsäure;

R_6 = H oder eine aliphatische, aromatische, acylalyphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

R_7 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

wobei wenigstens einer von R und R_5 eine Amidgruppe bildet,
mit der Maßgabe, dass die amidische, wasserlösliche Verbindung nicht über eine Amidbindung mit einem medizinischen Ingredienz kombiniert ist,
zur Herstellung von Salzen mit pharmakologisch aktiven Substanzen.

28. Verwendung von amidischen, wasserlöslichen Verbindungen von Hyaluronsäure oder einem Derivat davon, umfassend wenigstens eine Repetiereinheit der folgenden allgemeinen Formel:



worin:

R = NR_6R_7 oder eine alkoholische Gruppe der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe, OH, O-, eine alkoholische Gruppe von Hyaluronsäure, eine Aminogruppe von deacylierter Hyaluronsäure;

R_1, R_2, R_3, R_4 = H, SO_3-, Acylgruppe, die von einer carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, -CO- $(CH_2)_2$-COOY, Y = negative Ladung oder H;

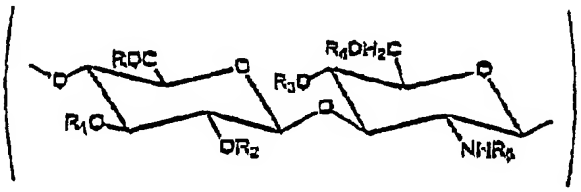
R_5 = -CO-CH_3, H, SO_3-, eine Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, eine Acylgruppe von Hyaluronsäure;

R_6 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

R_7 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

wobei wenigstens einer von R und R_5 eine Amidgruppe bildet,
allein oder in Kombination miteinander und/oder mit pharmakologisch aktiven Substanzen zur Herstellung von pharmazeutischen Zusammensetzungen, Biomaterialien, chirurgischen Gegenständen und Gegenständen für die Gesundheitsfürsorge, Systemen mit langsamer Freisetzung und Systeme für die Beschichtung biomedizinischer Gegenstände, mit der Maßgabe, dass die wasserlösliche amidische Verbindung nicht über eine Amidbindung mit einem medizinischen Ingredienz verbunden ist.

29. Verwendung von amidischen, wasserlöslichen Verbindungen von Hyaluronsäure oder einem Derivat davon, umfassend wenigstens eine Repetiereinheit der folgenden allgemeinen Formel:



worin:

R = NR_6R_7 oder eine alkoholische Gruppe der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe, OH, O-, eine alkoholische Gruppe von Hyaluronsäure, eine Amynogruppe von deacylierter Hyaluronsäure;

R_1, R_2, R_3, R_4 = H, SO_3-, Acylgruppe, die von einer Carbonsäuse der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, -CO- $(CH_2)_2$-COOY, Y = negative Ladung oder H;

R_5 = -CO-CH_3, H, SO_3-, eine Acylgruppe, die von einer Carbonsäure der aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe abgeleitet ist, eine Acylgruppe von Hyaluronsäure;

R_6 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

R_7 = H oder eine aliphatische, aromatische, arylaliphatische, cycloaliphatische oder heterocyclische Gruppe, die substituiert oder unsubstituiert ist;

wobei wenigstens einer von R und R_5 eine Amidgruppe bildet,
in Kombination mit radioaktiven und nicht radioaktiven Substanzen, die in Kontrastsystemen als Markierungen bei der in vivo-Diagnostik zur Identifizierung und Behandlung von Tumor-geweben oder geschädigten Geweben verwendet werden, mit der Maßgabe, dass die amidische, wasserlösliche Verbindung nicht über eine Amidbindung mit einem modizinischen Ingredienz kombiniert ist.

30. Verwendung der amidischen Verbindungen und ihrer Salze nach Anspruch 28, wobei die Biomaterialien in Form von Führungskanälen, Gazen, Fäden, Gelen, Hydrogelen, Tampons, Filman, Membranen, Schwämmen, Faservliesen, Mikrokügelchen, Nanokügelchen und Kombination derselben vorliegen.

31. Verwendung der amidischen Verbindung nach den vorängehenden Ansprüchen in der Chirurgie, Hämodialyse, Kardiologie, Dermatologie, Ophthalmologie, Otorhinolaryngologie, Zahnmedizin, Orthopädie, Gynäkologie, Urologie, im extrakorporalen Blutkreislauf und bei der extrakorporalen Oxygenation, in Kosmetika und in der Angiologie.

32. Verwendung der Amidverbindungen nach Anspruch 31, wobei die Chirurgie bedeutet innere Chirurgie, osteoartikuläre Chirurgie, Neurochirurgie, Anastomosenchirurgie, viskoelastische, ophthamische, onkologische, plastischästhetische, otorhinolaryngologische Chirurgie, Abdomen-Becken-Chirurgie, urogynäkologische, kardiovaskuläre Chirurgie, zum Beispiel bei der Herstellung von Herzklappen, Gefäßstents, bei der Prävention von Adhäsionen nach Chirurgie und bei hypertropher Vernarbung.

33. Verwendung von Biomaterialien nach den Ansprüchen 14 bis 17 in Verbindung mit Fibrin und gegebenenfalls mit anderen biologisch aktiven Substanzen zur Herstellung von chirurgischen Leimen.

34. Verwendung von Biomaterialien nach den Ansprüchen 14 bis 17 zur Herstellung von Gerüsten für Zellkulturen.

35. Verfahren zur Herstellung von Amiden am Stickstoff von Hyaluronsäure oder einem deacetylierten Derivat davon, umfassend die folgenden Schritte:

a) Deacetylierungsreaktion;
b) Herstellung des quaternären Ammoniumsalzes der deacetylierten Verbindung:
e) Herstellung des Acylierungsagenzes in Form eines aktiven Esters;
d) N-Acylierungsreaktion zwischen dem quaternären Ammoniumsalz von Hyalurensäure oder einem deacetylierten Derivat davon und dem Acylierungsmittel.

36. Verfahren nach Anspruch 35, wobei die Deacetylierungsreaktion durch Verwendung von Hydrazinsulfat/Hydrazin erreicht wird.

37. Verfahren nach Anspruch 35, wobei das quaternäre Ammoniumsalz das Tetrabutylammoniumsalz ist.

38. Verfahren nach Anspruch 35, wobei der aktive Ester der Paranitrophenylester einer aliphatischen, aromatischen, arylaliphatischen, cycloaliphatischen, heterocyclischen Säure, die zur Bildung des Amids ausgewählt wurde, ist.

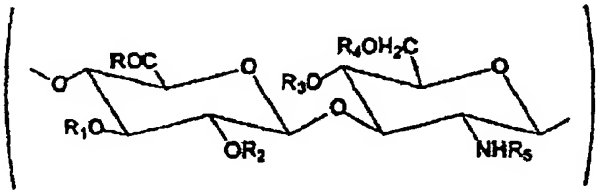
39. Verfahren zur Herstellung der amidischen, wasserlöslichen Verbindungen nach Anspruch 1, die die Amide an der Carboxylgruppe von Hyaluronsäure oder einem Derivat davon umfassen, umfassend die folgenden Schritte:

a) Aktivierung der Carboxygruppe durch Reaktion derselben in der Säureform oder als quaternäres Ammoniumsalz mit einem Aktivierungsmittel in saurer Lösung oder an einem sauren Harz;
b) Reaktion mit einem Amin der aliphatischen, aromatischen arylaliphatischen, cycloaliphatischen, heterocyclischen Reihe.

40. Verfahren nach Anspruch 39, wobei das Aktivierungsmittel 1,1-Carbonyldiimidazol ist.

Revendications

1. Composés amidiques hydrosolubles de l'acide hyaluronique ou d'un dérivé de celui-ci comprenant au moins une unité de répétition de formule générale suivante :



dans laquelle :

R = NR_6R_7, ou un groupe alcoolique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, OH, O-, un groupe alcoolique de l'acide hyaluronique, un groupe amino de l'acide hyaluronique désacylé ;
R_1, R_2, R_3, R_4 = H, SO_3^-, un groupe acyle dérivé d'un acide carboyxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, $-CO-(CH_2)_2-COOY$; Y = charge négative, ou H ;
R_5 = $-CO-CH_3$, H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, un groupe acylique de l'acide hyaluronique ;
R_6 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;
R_7 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;

dans laquelle au moins l'un parmi R ou R_5 forme un groupe amide, à condition que lorsque R_6 est H, R_7 n'est pas $-CH_2CO_2CH_3$, et que le composé amidique hydrosoluble ne soit pas combiné avec un ingrédient médicinal par l'intermédiaire d'une liaison amide.

2. Composés amidiques hydrosolubles obtenus par réaction des groupes carboxyliques de l'acide hyaluronique avec un groupe amino de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique destinés à être utilisés en ophtalmologie et en chirurgie ophtalmique.

3. Composés amidiques selon la revendication 1, dans lesquels les dérivés de l'acide hyaluronique sont des esters totaux ou partiels avec des alcools aliphatiques, aromatiques, arylaliphatiques, cycloaliphatiques ou hétéroaliphatiques.

4. Composés amidiques selon la revendication 1, dans lesquels les dérivés de l'acide hyaluronique sont des composés réticulés dans lesquels une partie ou tous les groupes carboxy du résidu D-glucuronique forment des esters intra ou intermoléculaires avec les fonctions alcooliques de la même chaîne polysaccharidique ou d'autres chaînes respectivement.

5. Composés amidiques selon la revendication 1, dans lesquels les dérivés de l'acide hyaluronique sont des composés réticulés dans lesquels une partie ou tous les groupes carboxy du résidu D-glucuronique sont tels qu'ils réagissent avec des polyalcools de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, générant une réticulation à l'aide de chaînes espaceurs.

6. Composés amidiques selon la revendication 1, transformés en sels avec des métaux lourds.

7. Composés amidiques selon la revendication 6, dans lesquels les métaux lourds sont ceux du 4ème, 5ème et 6ème groupe du tableau de classification des éléments et de préférence l'argent, le cobalt, le fer, le cuivre, le zinc, l'arsenic, le strontium, le zirconium, l'antimoine, l'or, le césium, le tungstène, le sélénium, le platine, le ruthénium, le bismuth, l'étain, le titane et le mercure.

8. Composés amidiques selon les revendications 1 à 7, transformés en sels avec des substances pharmacologiquement actives.

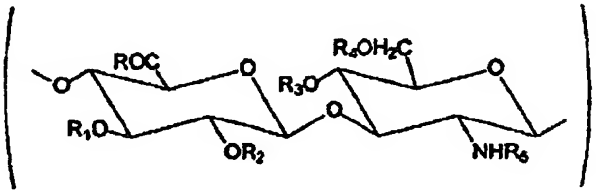
9. Composés amidiques selon la revendication 8, dans lesquels les substances pharmacologiquement actives sont des antibiotiques, des anti-infectieux, des antimicrobiens, des antiviraux, des cytostatiques, des antitumoraux, des anti-inflammatoires, des agents de cicatrisation des blessures, des anesthésiques, des agonistes et des antagonistes cholinergiques ou adrénergiques, des antithrombiques, des anticoagulants, des hémostatiques, des fibrinolytiques, des thrombolytiques, des protéines et leurs fragments, des peptides, des polynucléotides.

10. Composés amidiques et leurs sels selon les revendications 1 à 9, seuls ou en association les uns avec les autres et/ou avec des substances pharmacologiquement actives pour la préparation de compositions pharmaceutiques.

11. Composés amidiques et leurs sels selon la revendication 10, dans lesquels les substances pharmacologiquement actives sont des antibiotiques, des anti-infectieux, des antimicrobiens, des antiviraux, des cytostatiques, des antitumoraux, des anti-inflammatoires, des agents de cicatrisation des blessures, des anesthésiques, des agonistes ou des antagonistes cholinergiques ou adrénergiques, des antithrombiques, des anticoagulants, des hémostatiques, des fibrinolytiques, des thrombolytiques, des protéines et leurs fragments, des peptides, des polynucléotides, des facteurs de croissance, des enzymes, des vaccins, des substances utilisées dans le traitement des maladies associées à des défauts génétiques, des maladies déformantes et des maladies héréditaires.

12. Composés amidiques selon les revendications précédentes, en association avec des substances radioactives ou non radioactives, utilisés dans des systèmes de contraste en tant que marqueurs pour le diagnostic in vivo afin d'identifier et de traiter des tissus tumoraux ou des tissus endommagés.

13. Compositions pharmaceutiques contenant des composés amidiques hydrosolubles de l'acide hyaluronique ou d'un dérivé de celui-ci comprenant au moins une unité de répétition de formule générale suivante :



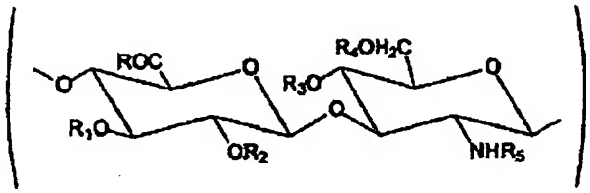
dans laquelle :

R = NR_6R_7, ou un groupe alcoolique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, OH, O-, un groupe alcoolique de l'acide hyaluronique, un groupe amino de l'acide hyaluronique

désacylé ;
R_1, R_2, R_3, R_4 = H, SO_3^-, un groupe acyle dérivé d'un acide carboyxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, $-CO-(CH_2)_2-COOY$; Y = charge négative, ou H ;
R_5 = $-CO-CH_3$, H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, un groupe acylique de l'acide hyaluronique ;
R_6 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;
R_7 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;

dans laquelle au moins un parmi R ou R_5 forme un groupe amide, seuls ou en association les uns avec les autres ou avec d'autres substances pharmacologiquement actives et en association avec un support pharmaceutiquement acceptable, à condition que le composé amidique hydrosoluble ne soit pas combiné avec un ingrédient médicinal par l'intermédiaire d'une liaison amide.

14. Biomatériaux à base de composés amidiques hydrosolubles de l'acide hyaluronique ou d'un dérivé de celui-ci comprenant au moins une unité de répétition de formule générale suivante :



dans laquelle :

R = NR_6R_7, ou un groupe alcoolique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, OH, O-, un groupe alcoolique de l'acide hyaluronique, un groupe amino de l'acide hyaluronique désacylé ;
R_1, R_2, R_3, R_4 = H, SO_3^-, un groupe acyle dérivé d'un acide carboyxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, $-CO-(CH_2)_2-COOY$; Y = charge négative, ou H ;
R_5 = $-CO-CH_3$, H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, un groupe acylique de l'acide hyaluronique ;
R_6 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;
R_7 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;

dans laquelle au moins un parmi R ou R_5 forme un groupe amide,
seuls ou en association les uns avec les autres ou avec d'autres polymères naturels, semisynthétiques, synthétiques et, éventuellement, avec des substances biologiquement actives, à condition que le composé amidique hydrosoluble ne soit pas combiné avec un ingrédient médicinal par l'intermédiaire d'une liaison amide.

15. Biomatériaux selon la revendication 14, dans lesquels les polymères naturels sont le collagène, les coprécipités de collagène et de glycosaminoglycanes, la cellulose, les polysaccharides sous forme de gels tels que la chitine, le chitosan, la pectine ou l'acide pectique, l'agar, l'agarose, le xanthane, le gellane, l'acide alginique ou les alginates, les polymannanes ou les polyglycanes, l'amidon, les gommes naturelles.

16. Biomatériaux selon la revendication 14, dans lesquels les polymères semisynthétiques sont le collagène réticulé avec des agents tels que des aldéhydes ou des précurseurs d'aldéhydes, des acides dicarboxyliques ou leurs halogénures, des diamines, des dérivés de cellulose, l'acide hyaluronique, la chitine ou le chitosan, le gellane, le xanthane, la pectine ou l'acide pectique, les polyglycanes, les polymannanes, l'agar, l'agarose, la gomme naturelle ou les glycosaminoglycanes.

17. Biomatériaux selon la revendication 14, dans lesquels les polymères synthétiques sont l'acide polylactique, l'acide polyglycolique ou les copolymères de l'acide polyglycolique ou leurs dérivés, les polydioxanes, les polyphosphazènes, les résines polysulphoniques, les polyuréthanes, le PTFE.

18. Biomatériaux selon les revendications 14 à 17, en association avec la fibrine, et éventuellement avec d'autres substances biologiquement actives pour la préparation de colles chirurgicales.

19. Biomatériaux selon les revendications 14 à 17 pour la préparation d'échafaudages pour des cultures cellulaires.

20. Biomatériaux selon les revendications 14 à 17 pour la préparation d'articles chirurgicaux et de soins de santé.

21. Biomatériaux selon les revendications 14 à 17, sous forme de canaux de guidage, de gazes, de fils, de gels, d'hydrogels, de tampons, de films, de membranes, d'éponges, de tissus non-tissés, de microsphères, de nanosphères et associations de ceux-ci.

22. Articles chirurgicaux et de soins de santé selon la revendication 20, sous la forme des canaux de guidage, de gazes, de fils, de gels, d'hydrogels, de tampons, de films, de membranes, d'éponges, de tissus non-tissés, de microsphères ou de nanosphères.

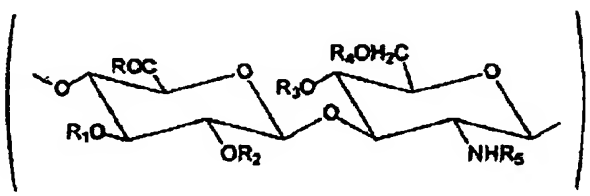
23. Biomatériaux selon les revendications 14 à 17 destinés à être utilisés en chirurgie, en hémodialyse, en cardiologie, en dermatologie, en ophtalmologie, en oto-rhino-laryngologie, en dentisterie, en orthopédie, en gynécologie, en urologie, dans le domaine de la circulation sanguine extra corporelle et l'oxygénation, en cosmétique ou en angiologie.

24. Biomatériaux selon la revendication 23 dans lesquels la chirurgie sous-entend la chirurgie interne ou ostéoarticulaire, la neurochirurgie, la chirurgie anastomotique, viscoélastique, ophtalmique, oncologique, plastique, esthétique, oto-rhino-laryngologique, abdomino-pelvienne, uro-gynécologique ou cardiovasculaire, telle que dans la préparation de valves cardiaques, d'endoprothèses vasculaires, dans la prévention des adhérences postchirurgicales et de la cicatrisation hypertrophique.

25. Composés amidiques et leurs sels selon les revendications 1 à 9 destinés au revêtement des objets biomédicaux tels que des déviations, des cathéters veineux, des anostomoses « shunts », des cathéters, des canaux de guidage, des sondes, des valves cardiaques, des tendons artificiels, des prothèses osseuses et cardiovasculaires, des lentilles de contact, des prothèses de tissu mou, des prothèses d'origine animale, des oxygénateurs de sang, des reins, des coeurs, des pancréas et des foies artificiels, des sacs sanguins, des seringues, des instruments chirurgicaux, des systèmes de filtration, des instruments de laboratoire, des récipients pour les cultures cellulaires et pour la régénération des cellules et des tissus, des supports pour les peptides, les protéines, les anticorps.

26. Utilisation des composés amidiques selon les revendications 7 à 8, en dermatologie, en ophtalmologie, en dentisterie, en stomatologie, en rhumatologie, en urologie, en gynécologie, en chirurgie interne, en tant que suppléments alimentaires, agents antioxydants, anti-rhumatismaux, anti-tumoraux, anti-inflammatoires, analgésiques ou anti-ulcéreux.

27. Utilisation des composés amidiques hydrosolubles de l'acide hyaluronique ou d'un dérivé de celui-ci comprenant au moins une unité de répétition de formule générale suivante :



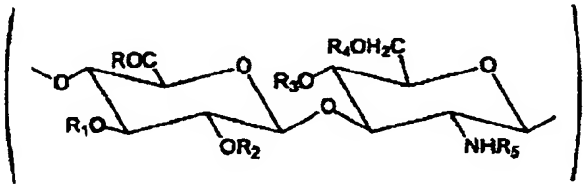
dans laquelle :

$R = NR_6R_7$, ou un groupe alcoolique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou

hétérocyclique, OH, O-, un groupe alcoolique de l'acide hyaluronique, un groupe amino de l'acide hyaluronique désacylé ;
R_1, R_2, R_3, R_4 = H, SO_3^-, un groupe acyle dérivé d'un acide carboyxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, $-CO-(CH_2)_2-COOY$; Y = charge négative, ou H ;
R_5 = $-CO-CH_3$, H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, un groupe acylique de l'acide hyaluronique ;
R_6 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;
R_7 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;

dans laquelle au moins l'un parmi R ou R_5 forme un groupe amide,
à condition que le composé amidique hydrosoluble ne soit pas combiné avec un ingrédient médicinal par l'intermédiaire d'une liaison amide,
pour la préparation de sels avec des substances pharmacologiquement actives.

28. Utilisation des composés amidiques hydrosolubles de l'acide hyaluronique ou d'un dérivé de celui-ci comprenant au moins une unité de répétition de formule générale suivante :

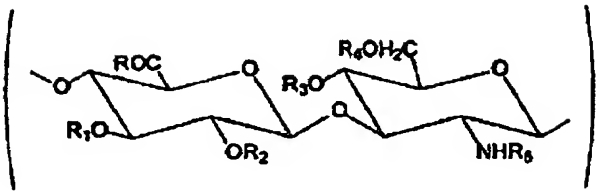


dans laquelle :

R = NR_6R_7, ou un groupe alcoolique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, OH, O-, un groupe alcoolique de l'acide hyaluronique, un groupe amino de l'acide hyaluronique désacylé ;
R_1, R_2, R_3, R_4 = H, SO_3^-, un groupe acyle dérivé d'un acide carboyxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, $-CO-(CH_2)_2-COOY$; Y = charge négative, ou H ;
R_5 = $-CO-CH_3$, H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, un groupe acylique de l'acide hyaluronique ;
R_6 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;
R_7 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;

dans laquelle au moins l'un parmi R ou R_5 forme un groupe amide, seuls ou en association les uns avec les autres et/ou avec des substances pharmaceutiquement actives pour la préparation de compositions pharmaceutiques, de biomatériaux, d'articles chirurgicaux et de soins de santé, de systèmes à libération lente et de systèmes destinés au revêtement des objets biomédicaux, à condition que le composé amidique hydrosoluble ne soit pas combiné avec un ingrédient médicinal par l'intermédiaire d'une liaison amide.

29. Utilisation des composés amidiques hydrosolubles de l'acide hyaluronique ou d'un dérivé de celui-ci comprenant au moins une unité de répétition de formule générale suivante :



dans laquelle :

R = NR_6R_7, ou un groupe alcoolique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, OH, O-, un groupe alcoolique de l'acide hyaluronique, un groupe amino de l'acide hyaluronique désacylé ;
R_1, R_2, R_3, R_4 = H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, $-CO-(CH_2)_2-COOY$; Y = charge négative, ou H ;
R_5 = $-CO-CH_3$, H, SO_3^-, un groupe acyle dérivé d'un acide carboxylique de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, un groupe acylique de l'acide hyaluronique ;
R_6 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;
R_7 = H ou un groupe aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, substitué ou non substitué ;

dans laquelle au moins l'un parmi R ou R_5 forme un groupe amide, en association avec des substances radioactives et non radioactives, utilisés dans des systèmes de contraste en tant que marqueurs pour le diagnostic in vivo afin d'identifier et de traiter des tissus tumoraux ou des tissus endommagés, à condition que le composé amidique hydrosoluble ne soit pas combiné avec un ingrédient médicinal par l'intermédiaire d'une liaison amide.

30. Utilisation des composés amidiques et de leurs sels selon la revendication 28, dans laquelle les biomatériaux sont sous forme de canaux de guidage, de gazes, de fils, de gels, d'hydrogels, de tampons, de films, de membranes, d'éponges, de tissus non tissés, de microsphères, de nanosphères et associations de ceux-ci.

31. Utilisation du composé amidique selon les revendications précédentes, en chirurgie, en hémodialyse, en cardiologie, en dermatologie, en ophtalmologie, en oto-rhino-laryngologie, en dentisterie, en orthopédie, en gynécologie, en urologie, dans le domaine de la circulation sanguine extra corporelle et l'oxygénation, en cosmétique ou en angiologie.

32. Utilisation des composés amidiques selon la revendication 31, où la chirurgie sous-entend la chirurgie interne ou ostéoarticulaire, la neurochirurgie, la chirurgie anastomotique, viscoélastique, ophtalmique, oncologique, plastique, esthétique, oto-rhino-laryngologique, abdomino-pelvienne, uro-gynécologique, cardiovasculaire, telle que dans la préparation de valves cardiaques, d'endoprothèses vasculaires, dans la prévention d'adhésions postchirurgicales et de la cicatrisation hypertrophique.

33. Utilisation des biomatériaux selon les revendications 14 à 17, en association avec la fibrine, et éventuellement avec d'autres substances biologiquement actives pour la préparation de colles chirurgicales.

34. Utilisation des biomatériaux selon les revendications 14 à 17 pour la préparation d'échafaudages pour des cultures cellulaires.

35. Procédé de préparation d'amides sur l'azote de l'acide hyaluronique ou d'un dérivé désacétylé de celui-ci mettant en jeu les étapes suivantes :

a) réaction de desacétylation ;
b) préparation du sel d'ammonium quaternaire du composé desacétylé ;
c) préparation de l'agent d'acylation sous forme d'un ester actif ;
d) réaction de N-acylation entre le sel d'ammonium quaternaire de l'acide hyaluronique ou un dérivé desacétylé de celui-ci et l'agent d'acylation.

36. Procédé selon la revendication 35, dans lequel la réaction de desacétylation est obtenue en utilisant un mélange sulphate d'hydrazine/hydrazine.

37. Procédé selon la revendication 35, dans lequel le sel d'ammonium quaternaire est le sel de tétrabutylammonium.

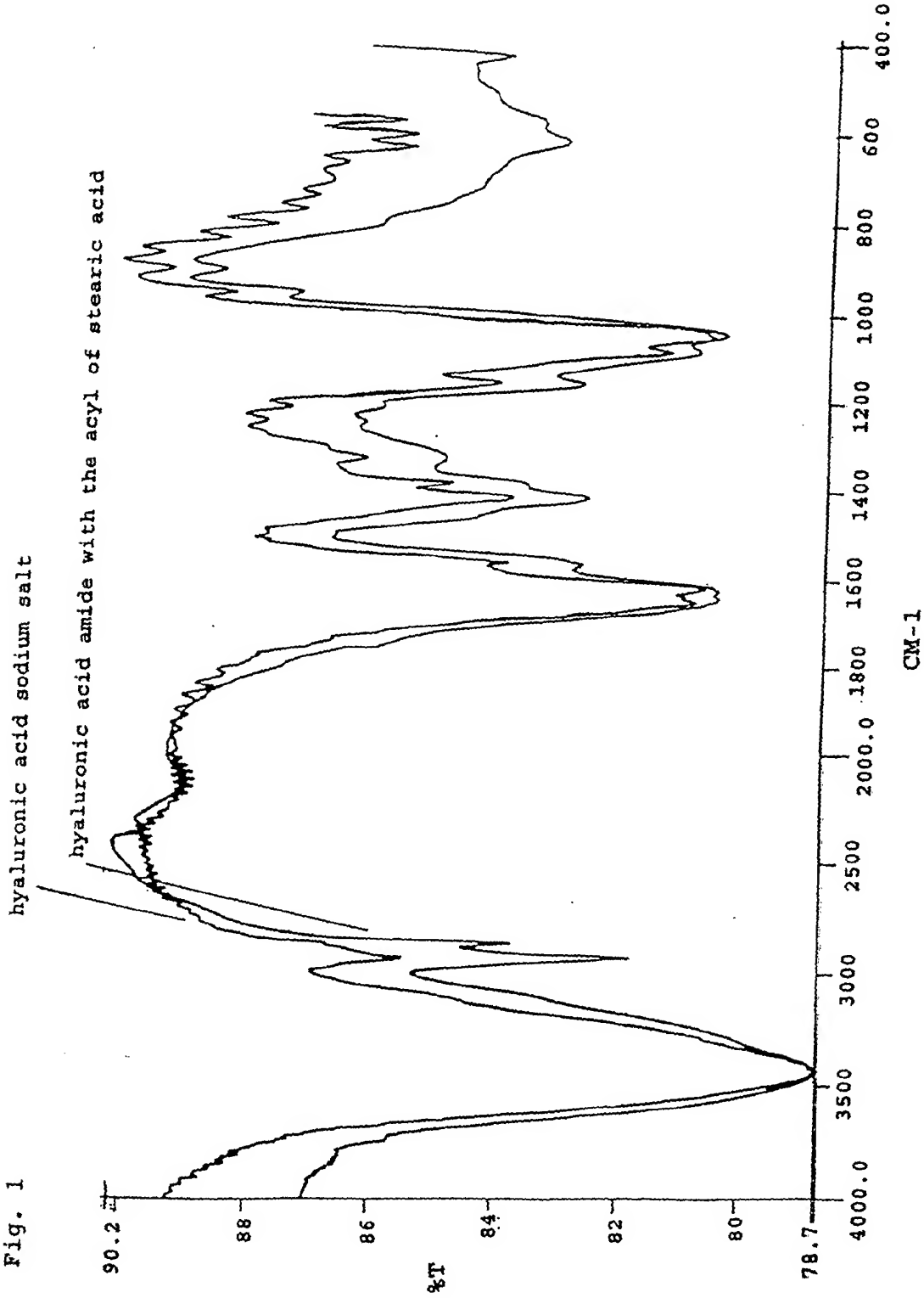
38. Procédé selon la revendication 35, dans lequel l'ester actif est l'ester paranitrophénylique d'un acide aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique, choisi pour la formation de l'amide.

39. Procédé de préparation des composés amidiques hydrosolubles selon la revendication 1 ayant les amides sur le carboxyle de l'acide hyaluronique ou d'un dérivé de celui-ci, mettant en jeu les étapes suivantes :

a) activation des groupes carboxy par réaction de ceux-ci, sous la forme acide ou d'un sel d'ammonium quaternaire, avec un agent d'activation, dans une solution acide ou sur une résine acide ;
b) réaction avec une amine de la série aliphatique, aromatique, arylaliphatique, cycloaliphatique ou hétérocyclique.

40. Procédé selon la revendication 39, dans lequel l'agent d'activation est le 1,1-carbonyldiimidazole.

Fig. 1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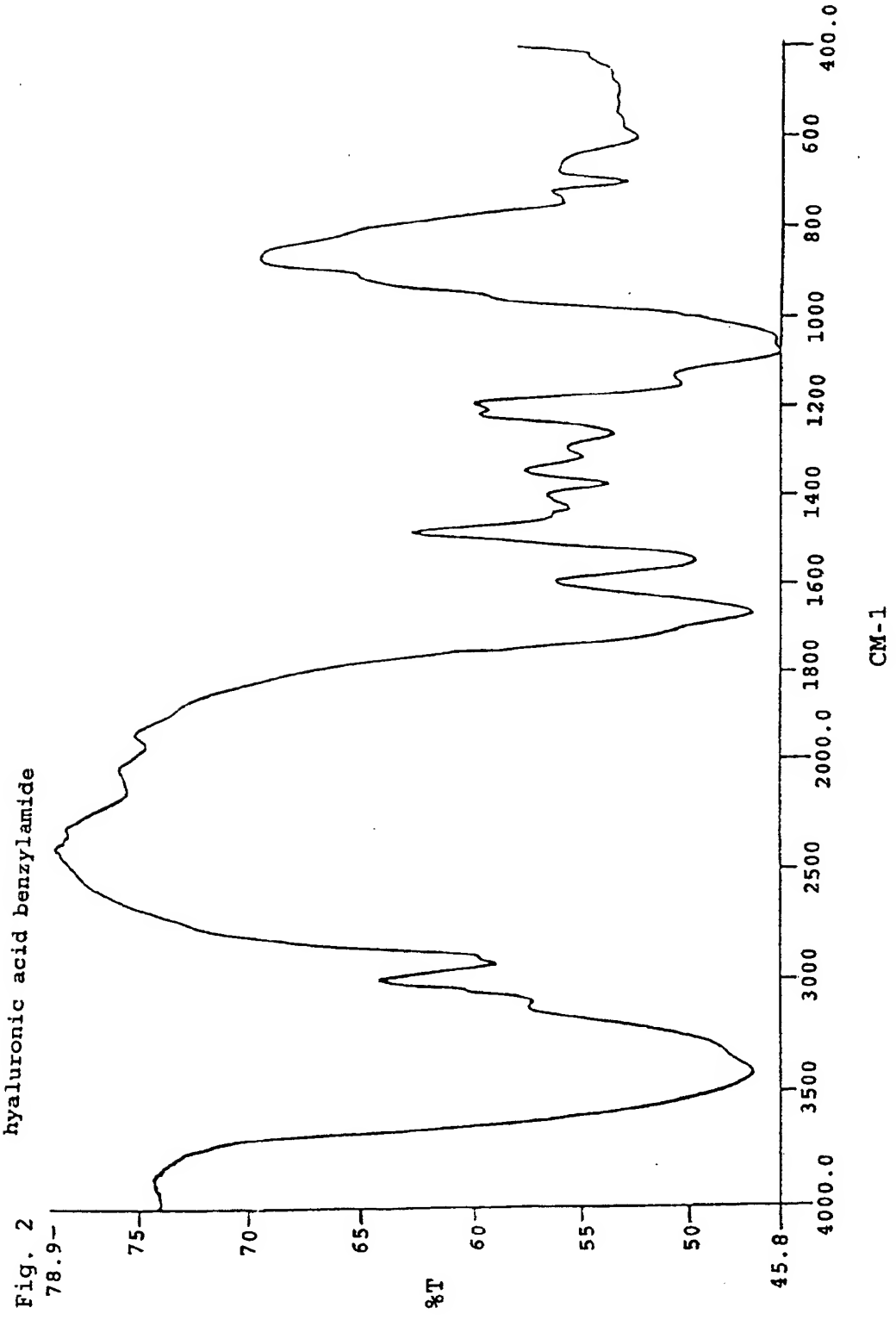
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Fig. 2

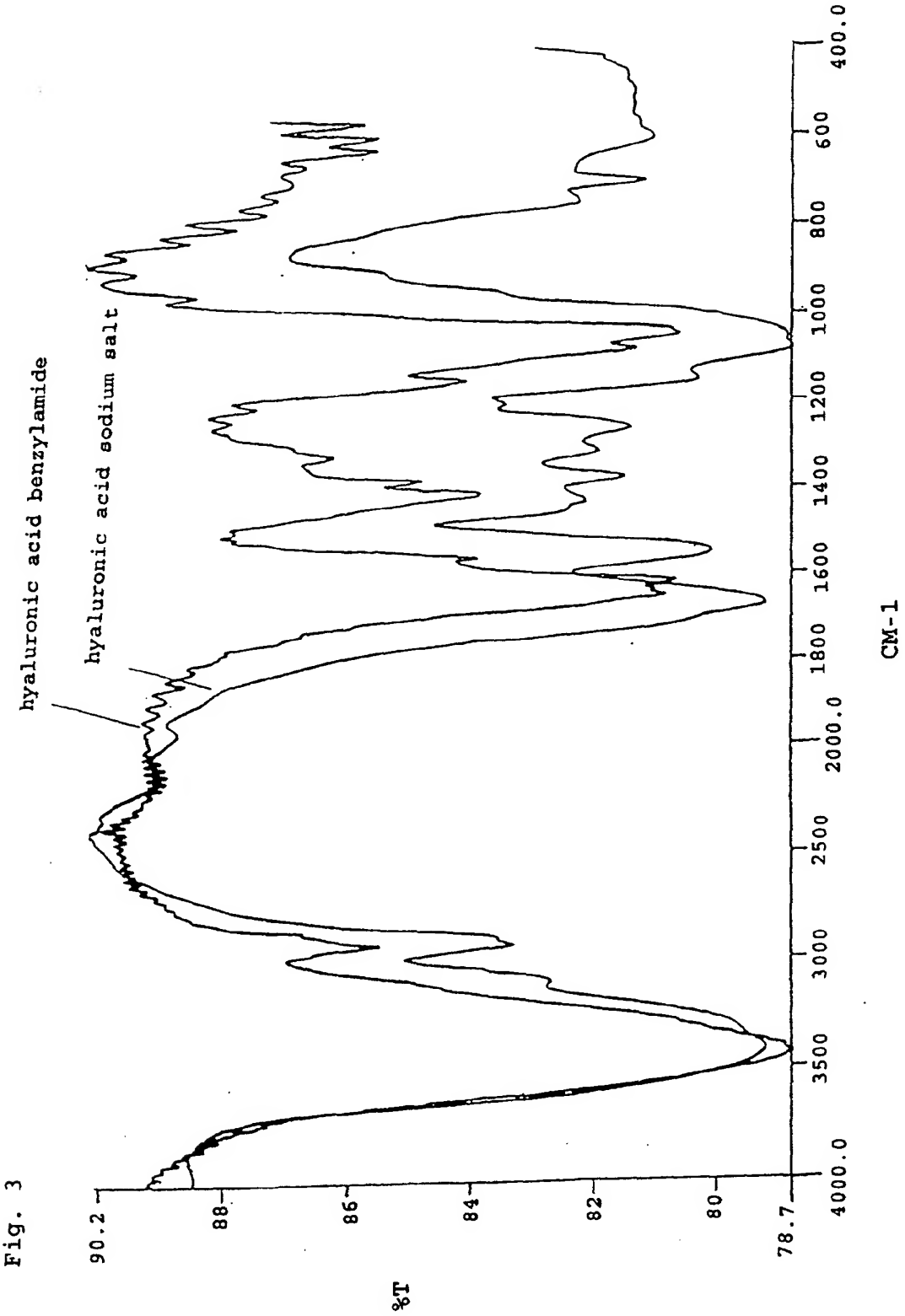
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Fig. 3